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# INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6:
C12N 15/55, 9/22, A61K 38/46

(43) International Publication Date: 29 August 1996 (29.08.96)

(21) International Application Number: PCT/US96/02421

(22) International Filing Date: 21 February 1996 (21.02.96)

(30) Priority Data:

PCT/US95/02366 24 February 1995 (24.02.95) WO
(34) Countries for which the regional or
international application was filed: KE et al.
08/540,527 10 October 1995 (10.10.95) US

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#### Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

### (54) Title: HUMAN DNASE I VARIANTS

#### (57) Abstract

The present invention relates to amino acid sequence variants of human DNase I that have reduced binding affinity for actin. The invention provides nucleic acid sequences encoding such actin-resistant variants, thereby enabling the production of these variants in variants of human DNase I.

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#### **HUMAN DNASE I VARIANTS**

#### Field of the Invention

The present invention is related to results obtained from research on human deoxyribonuclease I (DNase I), a phosphodiesterase that is capable of hydrolyzing polydeoxyribonucleic acid. It relates generally to modified (variant) forms of human DNase I and their preparation by recombinant DNA methods, to pharmaceutical compositions by which their utility can be exploited clinically, and to methods of using these DNase I variants and compositions thereof.

#### Background of the Invention

DNase I is a phosphodiesterase capable of hydrolyzing polydeoxyribonucleic acid. DNase I has been purified from various species to various degrees.

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Bovine DNase I has been extensively studied biochemically. See e.g., Moore, in <u>The Enzymes</u> (Boyer, P.D., ed), pp. 281-296, Academic press, New York (1981). The complete amino acid sequence for bovine DNase I is known (Liao, et al., J. Biol. Chem. <u>248</u>:1489-1495 (1973); Oefner, et al., J. Mol. Biol. <u>192</u>:605-632 (1986); Lahm, et al., J. Mol. Biol. <u>221</u>:645-667 (1991)), and DNA encoding bovine DNase I has been cloned and expressed (Worrall, et al., J. Biol. Chem <u>265</u>:21889-21895 (1990)). The structure of bovine DNase I has been determined by X-ray crystallography. Suck, et al., EMBO J. <u>3</u>:2423-2430 (1984); Suck, et al., Nature <u>321</u>:620-625 (1986); Oefner, et al., J. Mol. Biol. <u>192</u>:605-632 (1986).

DNA encoding human DNase I has been isolated and sequenced and that DNA has been expressed in recombinant host cells, thereby enabling the production of human DNase I in commercially useful quantities. Shak, et al., Proc. Nat. Acad. Sci. <u>87</u>:9188-9192 (1990).

DNase I has a number of known utilities and has been used for therapeutic purposes. Its principal therapeutic use has been to reduce the viscoelasticity of pulmonary secretions (mucus) in such diseases as pneumonia and cystic fibrosis (CF), thereby aiding in the clearing of respiratory airways. See e.g., Lourenco, et al., Arch. Intern. Med. 142:2299-2308 (1982); Shak, et al., Proc. Nat. Acad. Sci. 87:9188-9192 (1990); Hubbard, et al., New Engl. J. Med. 326:812-815 (1992); Fuchs, et al., New Engl. J. Med. 331:637-642 (1994); Bryson, et al., Drugs 48:894-906 (1994). Mucus also contributes to the morbidity of chronic bronchitis, asthmatic bronchitis, bronchiectasis, emphysema, acute and chronic sinusitis, and even the common cold.

The pulmonary secretions of persons having such diseases are complex materials, that include mucus glycoproteins, mucopolysaccharides, proteases, actin, and DNA. Some of the materials in pulmonary secretions are released from leukocytes (neutrophils) that infiltrate pulmonary tissue in response to the presence of microbes (e.g., strains of Pseudomonas, Pneumococcus, or Staphylococcus bacteria) or other irritants (e.g., tobacco smoke, pollen). In the course of reacting with such microbes or irritants, the leukocytes may degenerate and release their contents, which contribute to the viscoelasticity of the pulmonary secretions.

The ability of DNase I to reduce the viscoelasticity of pulmonary secretions has been ascribed to its enzymatic degradation of the large amounts of DNA released by neutrophils. Shak, et al., Proc. Nat. Acad. Sci. 87:9188-9192 (1990); Aitken, et al., J. Am. Med. Assoc. 267:1947-1951 (1992).

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More recently, a different mechanism has been proposed for the mucolytic effect of DNase I, involving disaggregation of actin. Vasconcellos, et al., Science 263:969-971 (1994). Actin is one of the most abundant proteins in eukaryotic cells (for example, actin comprises about 10% of total leukocyte protein) and has been extensively studied. Kabsch, et al., Ann. Rev. Biophys. Biomol. Struct 21:49-76 (1992): Sheterline, et al., Prot. Profile 1:1-121 (1994). Actin exists in two forms, a monomeric form (G-actin), and a filamentous form (F-actin) that is assembled from G-actin monomers. Polymeric filaments of actin are highly viscoelastic and contribute significantly to the viscosity of pulmonary secretions. Momet, et al., Proc. Nat. Acad. Sci. 81:3680-3684 (1984). Newman, et al., Biochemistry 24:1538-1544 (1985); Janmey, et al., Biochemistry 27:8218-8226 (1988). Vasconcellos, et al., Science 263:969-971 (1994).

Because DNase I is known to bind to actin (Lazarides, et al., Proc. Nat. Acad. Sci. 71:4742-4746 (1974); Kabsch, et al., Nature 347:37-44 (1990)) and to depolymerize actin filaments (as well as inhibit polymerization of G-actin into filaments) (Mannherz, et al., FEBS Lett. 60:34-38 (1975); Hitchcock, et al., Cell 7:531-542 (1976); Pinder, et al., Biochemistry 21:4886-4890 (1982); Weber, et al., Biochemistry 33:4780-4786 (1994)), it has been suggested that the mucolytic effect of DNase I on sputum and other pulmonary secretions is due to actin disaggregation (depolymerization) rather than to DNA hydrolysis. Vasconcellos, et al., Science 263:969-971 (1994). Consistent with this view, it is known that in the presence of actin, the DNA-hydrolytic activity of DNase I is inhibited. Lazarides, et al., Proc. Nat. Acad. Sci. 71:4742-4746 (1974); Mannherz, et al., Eur. J. Biochem. 104:367-379 (1980). Also consistent with this view, it has been reported that actin severing proteins (e.g., gelsolin) are effective in decreasing the viscoelasticity of cystic fibrosis sputum. Vasconcellos, et al., Science 263:969-971 (1994); Stossel, et al., PCT Patent Publication No. WO 94/22465 (published October 13, 1994).

The present invention is based in part on research by the inventors to determine the biochemical basis of the mucolytic activity of DNase I. This research involved the design and synthesis of various human DNase I variants, and the assay of these variants to assess their ability to hydrolyze DNA, to bind to actin, and to reduce the viscoelasticity of sputum in vitro. The inventors created several classes of human DNase I variants. One class of variants (actin-resistant variants) has decreased ability to bind actin, but still has mucolytic activity and in some cases had increased mucolytic activity as compared to native human DNase I. These actin-resistant variants have about the same DNA-hydrolytic activity as native human DNase I, but such activity is less susceptible to inhibition by actin. A second class of variants bind actin with an affinity similar to that found for native human DNase I, but have decreased mucolytic activity and decreased DNA-hydrolytic activity as compared to native human DNase I.

These results indicate that the therapeutic efficacy of human DNase I in reducing the viscoelasticity of pulmonary secretions is due to its catalytic, DNA-hydrolytic activity, rather than to its ability to depolymerize filamentous actin. Accordingly, variants of human DNase I that bind actin with lower affinity than native human DNase I, but that still possess DNA-hydrolytic activity should be useful therapeutic agents, especially in the treatment of patients having pulmonary secretions that comprise relatively large amounts of actin Because such variants have reduced affinity for actin, their DNA hydrolytic activity is less inhibited in the

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presence of actin, and so these variants have greater mucolytic activity in the presence of actin, as compared to native human DNase I.

It is therefore an object of the present invention to provide human DNase I variants that possess DNA-hydrolytic activity, but bind actin with lower affinity than native human DNase I.

It is another object of the invention to provide nucleic acids encoding such actin-resistant variants of human DNase I, recombinant vectors comprising such nucleic acids, recombinant host cells transformed with those nucleic acids or vectors, and processes for producing the human DNase I variants by means of recombinant DNA technology.

The invention also is directed to pharmaceutical compositions comprising the human DNase I actinresistant variants, optionally together with a pharmaceutically acceptable excipient.

The invention also is directed to a method for reducing the viscoelasticity or viscous consistency of DNA-containing material in a patient, comprising administering a therapeutically effective dose of an actin-resistant variant of DNase I to the patient.

The invention is particularly directed to a method of treating a patient having a disease such as cystic fibrosis, chronic bronchitis, pneumonia, bronchiectasis, emphysema, asthma, or systemic lupus erythematosus, that comprises administering a therapeutically effective amount of an actin-resistant variant of DNase I to the patient.

The invention also is directed to the use of actin-resistant variants of human DNase I in in vitro diagnostic assays of a viscous material (e.g., sputum) from a patient, to measure the amount of actin present and determine whether the patient is an appropriate candidate for treatment with an actin-resistant DNase I variant.

These and other objects of the invention will be apparent to the ordinary artisan upon consideration of the specification as a whole.

### Brief Description of the Figures

Figure 1 shows the amino acid sequence of human mature DNase I (SEQ. ID. NO: 1). The numbers indicate the sequential position of amino acid residues within the sequence.

Figures 2-6 show data for the following variants:

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		iits.	
A114C	(SEQ. ID. NO: 68)	D53R	(SEQ. ID. NO: 13)
A114B	(SEQ. ID. NO: 69)		
A114G			(SEQ. ID. NO: 14)
3114U		D58 <b>T</b>	(SEQ. ID. NO: 80)
		E13A	(SEQ. ID. NO: 2)
A114K	(SEQ. ID. NO: 72)	K13H	(SEQ. ID. NO: 3)
A114L	(SEQ. ID. NO: 73)		
A114M			(SEQ. ID. NO: 4)
		E13W	(SEQ. ID. NO: 5)
<del>-</del>		E13Y	(SEQ. ID. NO: 6)
A114R	(SEQ. ID. NO: 76)	<b>8691</b>	
A114W	(SEO. ID. NO. 77)		(SEQ. ID. NO: 65)
A114v		E69C	(SEQ. ID. NO: 66)
		E69K	(SEQ. ID. NO: 21)
-	(SEQ. ID. NO: 11)	<b>E</b> 69 <b>M</b>	(SEQ. ID. NO: 67)
D53C	(SEQ. ID. NO: 43)	F69b	
D53K			(SEQ. ID. NO: 22)
D531		G49C	(SEQ. ID. NO: 35)
		G491	(SEQ. ID. NO: 36)
D23W	(SEQ. ID. NO: 45)	G49K	(SEQ. ID. NO: 37)
	A114E A114G A114H A114K A114L A114M A114Q A114R A114W A114Y D53A D53C	Al14C (SEQ. ID. NO: 68) Al14B (SEQ. ID. NO: 69) Al14G (SEQ. ID. NO: 70) Al14H (SEQ. ID. NO: 71) Al14K (SEQ. ID. NO: 72) Al14L (SEQ. ID. NO: 73) Al14M (SEQ. ID. NO: 73) Al14M (SEQ. ID. NO: 74) Al14Q (SEQ. ID. NO: 75) Al14R (SEQ. ID. NO: 76) Al14W (SEQ. ID. NO: 77) Al14Y (SEQ. ID. NO: 78) D53A (SEQ. ID. NO: 78) D53C (SEQ. ID. NO: 43) D53K (SEQ. ID. NO: 12) D53L (SEQ. ID. NO: 44)	Al14E (SEQ. ID. NO: 69)  Al14G (SEQ. ID. NO: 70)  Al14H (SEQ. ID. NO: 71)  Al14K (SEQ. ID. NO: 72)  Al14L (SEQ. ID. NO: 73)  Al14L (SEQ. ID. NO: 73)  Al14M (SEQ. ID. NO: 74)  Al14Q (SEQ. ID. NO: 75)  Al14R (SEQ. ID. NO: 75)  Al14R (SEQ. ID. NO: 76)  Al14W (SEQ. ID. NO: 77)  Al14Y (SEQ. ID. NO: 77)  B69C  Al14Y (SEQ. ID. NO: 78)  D53A (SEQ. ID. NO: 11)  B69M  D53C (SEQ. ID. NO: 43)  B69R  D53L (SEQ. ID. NO: 12)  G49I

	G4 9R	(SEQ. ID. NO:	38)	V67A	(SEÇ.	ID.	NO	18)
	G4 9 Y	(SEQ. ID. NO:			(SEQ.	ID.	NO	55)
	H44A	(SEQ. ID. NO:		V67D	(SEQ.	ID.	: C <b>1</b>	56)
	H44C	(SEQ. ID. NO:		V67E	(SEQ.	ID.	$\mathbf{NO}:$	19)
5	H44D	(SEQ. ID. NO:	8)	V67H	(SEQ.	ID.	$\mathbf{N}\bigcirc:$	57,
J	H44E	(SEQ. ID. NO:	86)	V67K	(SEÇ.	ID.	<b>и</b> 0 :	20)
	H44N	(SEQ. ID. NO:	79)	V67 <b>M</b>	(SEQ.		NC:	
	H44Q	(SEQ. ID. NO:	29)	V67P	(SEQ.		и⊖ :	
	H44W	(SEQ. ID. NO:	10)	V67R	(SEQ.		NO:	
10	H44Y	(SEQ. ID. NO:	9)	V678	(SEQ.		NO:	
	L45C	(SEQ. ID. NO:	30)	Y65A	(SEQ.		NO:	
	L45K	(SEQ. ID. NO:	31)	Y65C	(SEQ.		NC:	
	L45R	(SEQ. ID. NO:		¥65 <b>B</b>	(SEQ.		NC:	
	L52C	(SEQ. ID. NO:		¥65K	(SEQ.		NC:	
15	L52K	(SEQ. ID. NO:		Y65M	(SEQ.		NO:	53) 97)
	L52M	(SEQ. ID. NO:		Y65P	(SEQ.	ID.	NO.	
	L52N	(SEQ. ID. NO:		Y65R	(SEQ.			54)
	L52R	(SEQ. ID. NO:		Y658	(SEQ.			17)
	N56C	(SEQ. ID. NO:		Y65W D53R:B69R	_			25)
20	<b>N</b> 56C	(SEQ. ID. NO:		D53R:B69R				
	N56F	(SEQ. ID. NO:		D53R:H4A				
	N56F	(SEQ. ID. NO:		H64N:V66T			NO:	
	N56K	(SEQ. ID. NO:		S68N:P70T				
	N56K	(SEQ. ID. NO: (SEQ. ID. NO:			(SEQ.		NO:	
25	N56R	(SEQ. ID. NO: (SEQ. ID. NO:		<del></del>	(SEQ.			
	N56R N56W	(SEQ. ID. NO:		Y65N:V67T				
	N56W	(SEQ. ID. NO:		D53R:Y65A:				
	868K	(SEQ. ID. NO		88)		(029.		
30	S68M	(SEQ. ID. NO		H44A:D53R	Y65A	(SEC.	. ID.	NO:
30	368R	(SEQ. ID. NO		26)		·		
	V48C	(SEQ. ID. NO		H44A:Y65A	: E69R	(SEQ	. ID	. <b>N</b> O:
	V48K	(SEQ. ID. NO		27)		_		
	V48R	(SEQ. ID. NO	: 89)	<del>-</del> · ,				
35	V66N	(SEQ. ID. NO						

Figures 2A-D show the relative specific activity of native human DNase I and variants. The error bars represent the standard deviation (n-weighted). The relative specific activity of Pulmozyme& human DNase I (Genentech, Inc., South San Francisco, California USA) is defined as 1.0. The relative specific activity of native human DNase I is greater than that of Pulmozyme® due to the occurrence in Pulmozyme® of a deamidated form of human DNase I that has reduced DNA-hydrolytic activity (Frenz, et al., PCT Patent Publication No WO 93/25670, published December 23, 1993).

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Figure 3 shows the DNA-hydrolytic activity of native human DNase I and single-residue variants of human DNase I in the presence of actin, as determined in a hyperchromicity assay. "Percent activity" is the percent DNA-hydrolytic activity of the DNase I (native or variant) calculated as described in Example 3: the DNA-hydrolytic activity of the DNase I in the absence of actin is defined as 100 percent activity. The error bars represent the standard deviation.

Figure 4 shows the DNA-hydrolytic activity of native human DNase I and multiple-residue variants of human DNase I in the presence of actin, as determined in a hyperchromicity assay or a methyl green assay. "Percent activity" is the percent DNA-hydrolytic activity of the DNase I (native or variant) calculated as described in Example 3; the DNA-hydrolytic activity of the DNase I in the absence of actin is defined as 100 percent activity. The error bars represent the standard deviation.

Figures 5A-D show the relative binding affinity of human DNase I variants for actin as determined in an actin binding ELISA assay (as described in Example 3). The EC<sub>50</sub> value is the concentration of the DNase I (native or variant) that is required to give a half-maximal signal in the assay. The error bars represent the standard deviation. The EC<sub>50</sub> values for Pulmozyme® and native human DNase I are  $67 \pm 23$  pM (n = 31) and  $87 \pm 14$  pM (n = 32), respectively. The relative binding affinity shown in the figure is the EC<sub>50</sub> value determined for the human DNase I variant divided by the EC<sub>50</sub> value determined for native human DNase I. Variants where the EC<sub>50</sub> value was larger than could be measured in the assay are indicated as having a ratio (EC<sub>50</sub> (DNasel variant)/EC<sub>50</sub> (native DNase I)) greater than a certain value (for example, >10, >100, >300, >2000, >20,000, >35,000).

Figure 6 shows the mucolytic activity of native human DNase I and variants of human DNase I in sputum samples from cystic fibrosis patients, as determined by a compaction assay. The error bars represent the standard error of the mean.

Figure 7 shows a schematic representation of the actin binding ELISA assay described in Example 3

#### Detailed Description

#### 20 I. <u>Definitions</u>

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As used herein, the terms "human DNase I", "native human DNase I", and "wild-type DNase I" refer to the polypeptide having the amino acid sequence of human mature DNase I set forth in Figure 1.

A "variant" or "amino acid sequence variant" of human DNase I is a polypeptide that comprises an amino acid sequence different from that of native human DNase I. Generally, a variant will possess at least 80% sequence identity (homology), preferably at least 90% sequence identity, more preferably at least 95% sequence identity, and most preferably at least 98% sequence identity with native human DNase I. Percentage sequence identity is determined, for example, by the Fitch, et al., Proc. Nat. Acad. Sci. USA 80:1382-1386 (1983), version of the algorithm described by Needleman, et al., J. Mol. Biol. 48:443-453 (1970), after aligning the sequences to provide for maximum homology

The terms "human DNase I actin-resistant variant", "actin-resistant variant", and "actin-resistant variant of human DNase I" refer to a variant of native human DNase I that has (1) DNA-hydrolytic activity and (2) reduced binding affinity for actin.

"DNA-hydrolytic activity" refers to the enzymatic activity of native human DNase I or a variant of human DNase I in hydrolyzing (cleaving) substrate DNA to yield 5'-phosphorylated oligonucleotide end products. DNA-hydrolytic activity is readily determined by any of several different methods known in the art, including analytical polyacrylamide and agarose gel electrophoresis, hyperchromicity assay (Kunitz, J. Gen.

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Physiol. 33:349-362 (1950); Kunitz, J. Gen. Physiol. 33:363-377 (1950)), or methyl green assay (Kurnick Arch. Biochem. 29:41-53 (1950); Sinicropi, et al., Anal. Biochem. 222:351-358 (1994))

The "binding affinity" of native human DNase I or an actin-resistant variant of human DNase I for actin refers to the ability of the DNase I to noncovalently bind to actin. Binding affinity may be determined by any of various methods known in the art, for example, as described in Mannherz, et al., Eur. J. Biochem. 104 367-379 (1980). Alternatively, the relative binding affinities of different DNases (e.g., native human DNase I and variants thereof) are determined by measuring the binding of the DNases to immobilized actin in an ELISA assay (described in Example 3), or by comparing the DNA-hydrolytic activity of the DNases in the presence and absence of actin (also described in Example 3). The methods described in the Examples are especially convenient for screening variants of human DNase I to rapidly identify those variants that have a reduced binding affinity for actin.

A human DNase I actin-resistant variant having "reduced binding affinity for actin" is one having a binding affinity for actin that is relatively less than the affinity with which native human DNase I binds actin. determined under comparable conditions. If the actin binding ELISA assay as described in Example 3 is used to determine the binding affinity of a human DNase I (native or variant) for actin, then an actin-resistant variant having "reduced binding affinity for actin" will be one having an EC<sub>50</sub> value that is greater than that of native human DNase I. In that assay, an actin-resistant variant typically will have an EC<sub>50</sub> value five-fold to 100-fold greater than that of native human DNase; but actin-resistant variants having an EC<sub>50</sub> value over 500-fold greater than that of native human DNase I also are readily produced, especially by altering multiple amino acid residues of the native human DNase I amino acid sequence (see e.g., Figure 5A, 5D).

"Mucolytic activity" refers to the reduction of viscoelasticity (viscosity) of sputum or other biological material, for example as observed upon treatment of the material with native human DNase I or a variant of human DNase I. Mucolytic activity is readily determined by any of several different methods known in the art, including sputum compaction assay (PCT Patent Publication No. WO 94/10567, published May 11, 1994), assays using a torsion pendulum (Janmey, J. Biochem. Biophys. Methods 22:41-53 (1991), or other rheological methodologies.

"Polymerase chain reaction," or "PCR," generally refers to a method for amplification of a desired nucleotide sequence in vitro, as described, for example, in U.S. Pat. No. 4,683,195. In general, the PCR method involves repeated cycles of primer extension synthesis, using oligonucleotide primers capable of hybridizing preferentially to a template nucleic acid.

"Cell," "host cell," "cell line," and "cell culture" are used interchangeably herein and all such terms should be understood to include progeny resulting from growth or culturing of a cell. "Transformation" and "transfection" are used interchangeably to refer to the process of introducing DNA into a cell.

"Operably linked" refers to the covalent joining of two or more DNA sequences, by means of enzymatic ligation or otherwise, in a configuration relative to one another such that the normal function of the sequences can be performed. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide. a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence. or

a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous and, in the case of a secretory leader, contiguous and in reading phase. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, then synthetic oligonucleotide adaptors or linkers are used, in conjunction with standard recombinant DNA methods.

Amino acids are identified herein by three-letter or single-letter designations, as follows:

	Asp D aspartic acid	He I isoleucine
	Thr T threonine	Leu L leucine
	Ser S serine	Tyr Y tyrosine
10	Glu E glutamic acid	Phe F phenylalanine
	Pro P proline	His H histidine
	Gly G glycine	Lys K lysine
	Ala A alanine	Arg R arginine
	Cys C cysteine	Trp W tryptophan
15	Val V valine	Gln Q glutamine
	Met M methionine	Asn N asparagine

#### II. Selection of Actin-Resistant Variants

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The present invention is based upon the study of structure, actin binding properties, DNA-hydrolytic activity, and mucolytic activity of amino acid sequence variants of human DNase I. The actin-resistant variants of the present invention have DNA-hydrolytic activity, but bind actin with less affinity than native human DNase I. The reduction in actin binding preferably is achieved by making mutations at and/or around those amino acid residues within native human DNase I that appear to affect the binding of actin, including, for example, the Glu13, His44, Leu45, Val48, Gly49, Leu52, Asp53, Asn56, Asp58, His64, Tyr65, Val66, Val67, Ser68, Glu69, Pro70, Ser94, Tyr96, and Alal 14 residues of native human DNase I (the number following the three-letter amino acid designation indicates the specific position of the amino acid residue within the Figure 1 sequence).

There are a variety of ways in which one can make actin-resistant variants of human DNase I. In one embodiment of this invention, an actin-resistant variant is prepared by introducing either single or multiple amino acid substitutions, insertions, and/or deletions at or adjacent to (i.e., within about five amino acid residues of) those amino acid residues of native human DNase I that affect actin binding. Some illustrative examples of such mutations are as follows: D53R, D53K, D53Y, D53A, Y65A, Y65E, Y65R, V67E, V67K, E69R, D53R:Y65A, D53R:Y65A, D53R:Y65A, B44A:Y65A:E69R (see Figures 2-6).

In another embodiment of this invention, an actin-resistant variant is prepared by introducing mutation(s) that create a new glycosylation site at or adjacent to (i.e., within about five amino acid residues of) an amino acid residues of native human DNase I that affect actin binding. For example, site-directed mutagenesis is used to introduce one of the tripeptide sequences, asparagine-X-serine or asparagine-X-threonine (wherein X is any amino acid except proline), which are recognition sequences for enzymatic attachment of a

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carbohydrate moiety to the asparagine side chain. Creighton, <u>Proteins</u>, pp.76-78 (W.H. Freeman, 1984). Steric hindrance occurring between the carbohydrate moiety of the resulting N-glycosylated variant DNase I and actin can reduce or prevent actin binding and consequential inhibition of the DNase I DNA-hydrolytic activity, as compared to native human DNase I. Some illustrative examples of such mutations to introduce a new glycosylation site are as follows: H44N, D58S, D58T, V66N, H44N:T46S, H64N V66S, H64N V66T, Y65N:V67S, Y65N:V67T, V66N:S68T, V67N:E69S, V67N:E69T, S68N:P70S, S68N:P70T, S94N Y96S S94N:Y96T.

Optionally, in conjunction with such mutations to create a new glycosylation site, the naturally occurring glycosylation site at positions 18 and/or 106 within the native human DNase I amino acid sequence may be deleted, depending upon the extent of glycosylation desired in the actin-resistant variant.

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In a further embodiment of this invention, site-directed mutagenesis is used to introduce residues at or adjacent to (i.e., within about five amino acid residues of) those amino acid residues of native human DNase I that are involved in actin binding that are suitable for post-translational modification either biologically or chemically (see below). Means, et al., Chemical Modification of Proteins (Holden-Day, 1971); Glazer, et al., Chemical Modification of Proteins: Selected Methods and Analytical Procedures (Elsevier, 1975); Creighton. Proteins, pp.70-87 (W.H. Freeman, 1984); Lundblad, Chemical Reagents for Protein Modification (CRC Press 1991). Such post-translational modifications may introduce steric hinderance or altered electrostatic properties into the DNase I that will reduce or prevent actin binding and subsequent inhibition of DNA-hydrolytic activity, as compared to native human DNase I. For example, a cysteine residue may be introduced at or adjacent to a residue of native human DNase I that is involved in actin binding. The free thiol of the cysteine residue may form an intermolecular disulfide bond with another such DNase I variant to form a DNase I dimer, or may be modified, for example, with a thiol-specific alkylating agent. Some illustrative examples of such mutations are as follows: H44C, L45C, V48C, G49C, L52C, D53C, N56C, Y65C, V67C, E69C, A114C.

For convenience, substitutions, insertions, and/or deletions in the amino acid sequence of native human DNase I are usually made by introducing mutations into the corresponding nucleotide sequence of the DNA encoding native human DNase I, for example by site-directed mutagenesis. Expression of the mutated DNA then results in production of the variant human DNase I, having the desired (non-native) amino acid sequence.

Whereas any technique known in the art can be used to perform site-directed mutagenesis, e.g. as disclosed in Sambrook, et al., Molecular Cloning: A Laboratory Manual, Second Edition (Cold Spring Harbor Laboratory Press, New York (1989)), oligonucleotide-directed mutagenesis is the preferred method for preparing the human DNase I variants of this invention. This method, which is well known in the art (Zoller, et al., Meth. Enz. 100:4668-500 (1983); Zoller, et al., Meth. Enz. 154:329-350 (1987); Carter, Meth. Enz. 154:382-403 (1987); Kunkel, et al., Meth. Enzymol. 154:367-382 (1987); Horwitz, et al., Meth. Enz. 185:599-611 (1990)), is particularly suitable for making substitution variants, although it may also be used to conveniently prepare deletion and insertion variants.

The site-directed mutagenesis technique typically employs a phage vector that exists in both a single-stranded and double-stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage, and plasmid vectors that contain a single-stranded phage origin of replication (Messing, et

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al., Meth. Enzymol. 101:20-78 (1983); Veira et al., Meth. Enzymol. 153:3-11 (1987); Short, et al., Nuc. Acids. Res. 16:7583-7600 (1988)). Replication of these vectors in suitable host cells results in the synthesis of single-stranded DNA that may be used for site-directed mutagenesis.

Briefly, in carrying out site-directed mutagenesis of DNA encoding native human DNase I (or a variant thereof), the DNA is altered by first hybridizing an oligonucleotide encoding the desired mutation to a single strand of the DNA. After hybridization, a DNA polymerase is used to synthesize an entire second strand, using the hybridized oligonucleotide as a primer, and using the single strand of the DNA as a template. Thus, the oligonucleotide encoding the desired mutation is incorporated in the resulting double-stranded DNA.

Oligonucleotides for use as hybridization probes or primers may be prepared by any suitable method, such as by purification of a naturally occurring DNA or by in vitro synthesis. For example, oligonucleotides are readily synthesized using various techniques in organic chemistry, such as described by Narang, et al., Meth. Enzymol. 68:90-98 (1979); Brown, et al., Meth. Enzymol. 68:109-151 (1979); Caruthers, et al., Meth. Enzymol. 154:287-313 (1985). The general approach to selecting a suitable hybridization probe or primer is well known. Keller, et al., DNA Probes, pp.11-18 (Stockton Press, 1989). Typically, the hybridization probe or primer will contain 10-25 or more nucleotides, and will include at least 5 nucleotides on either side of the sequence encoding the desired mutation so as to ensure that the oligonucleotide will hybridize preferentially at the desired location to the single-stranded DNA template molecule.

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Of course, site-directed mutagenesis may be used to introduce multiple substitution, insertion, or deletion mutations into a starting DNA. If the sites to be mutated are located close together, the mutations may be introduced simultaneously using a single oligonucleotide that encodes all of the desired mutations. If, however, the sites to be mutated are located some distance from each other (separated by more than about ten nucleotides), it is more difficult to generate a single oligonucleotide that encodes all of the desired changes. Instead, one of two alternative methods may be employed

In the first method, a separate oligonucleotide is generated for each desired mutation. The oligonucleotides are then annealed to the single-stranded template DNA simultaneously, and the second strand of DNA that is synthesized from the template will encode all of the desired amino acid substitutions.

The alternative method involves two or more rounds of mutagenesis to produce the desired variant. The first round is as described for introducing a single mutation. The second round of mutagenesis utilizes the mutated DNA produced in the first round of mutagenesis as the template. Thus, this template already contains one or more mutations. The oligonucleotide encoding the additional desired amino acid substitution(s) is then annealed to this template, and the resulting strand of DNA now encodes mutations from both the first and second rounds of mutagenesis. This resultant DNA can be used as a template in a third round of mutagenesis, and so on.

PCR mutagenesis (Higuchi, in <u>PCR Protocols</u>, pp.177-183 (Academic Press, 1990); Vallette, et al., Nuc. Acids Res. <u>17</u>:723-733 (1989)) is also suitable for making the variants of human DNase I. Briefly, when small amounts of template DNA are used as starting material in a PCR, primers that differ slightly in sequence from the corresponding region in the template DNA can be used to generate relatively large quantities of a specific DNA fragment that differs from the template sequence only at the positions where the primers differ

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from the template. For introduction of a mutation into a plasmid DNA, for example, the sequence of one of the primers includes the desired mutation and is designed to hybridize to one strand of the plasmid DNA at the position of the mutation; the sequence of the other primer must be identical to a nucleotide sequence within the opposite strand of the plasmid DNA, but this sequence can be located anywhere along the plasmid DNA. It is preferred, however, that the sequence of the second primer is located within 200 nucleotides from that of the first, such that in the end the entire amplified region of DNA bounded by the primers can be easily sequenced PCR amplification using a primer pair like the one just described results in a population of DNA fragments that differ at the position of the mutation specified by the primer, and possibly at other positions, as template copying is somewhat error-prone. Wagner, et al., in PCR Topics, pp.69-71 (Springer-Verlag, 1991).

If the ratio of template to product amplified DNA is extremely low, the majority of product DNA fragments incorporate the desired mutation(s). This product DNA is used to replace the corresponding region in the plasmid that served as PCR template using standard recombinant DNA methods. Mutations at separate positions can be introduced simultaneously by either using a mutant second primer, or performing a second PCR with different mutant primers and ligating the two resulting PCR fragments simultaneously to the plasmid fragment in a three (or more)-part ligation.

Another method for preparing variants, cassette mutagenesis, is based on the technique described by Wells et al., Gene, 34:315-323 (1985). The starting material is the plasmid (or other vector) comprising the DNA sequence to be mutated. The codon(s) in the starting DNA to be mutated are identified. There must be a unique restriction endonuclease site on each side of the identified mutation site(s). If no such restriction sites exist, they may be generated using the above-described oligonucleotide-mediated mutagenesis method to introduce them at appropriate locations in the DNA. The plasmid DNA is cut at these sites to linearize it. A double-stranded oligonucleotide encoding the sequence of the DNA between the restriction sites but containing the desired mutation(s) is synthesized using standard procedures, wherein the two strands of the oligonucleotide are synthesized separately and then hybridized together using standard techniques. This double-stranded oligonucleotide is referred to as the cassette. This cassette is designed to have 5' and 3' ends that are compatible with the ends of the linearized plasmid, such that it can be directly ligated to the plasmid. The resulting plasmid contains the mutated DNA sequence.

The presence of mutation(s) in a DNA is determined by methods well known in the art, including restriction mapping and/or DNA sequencing. A preferred method for DNA sequencing is the dideoxy chain termination method of Sanger, et al., Proc. Nat. Acad. Sci. USA <u>72</u>:3918-3921 (1979).

DNA encoding a human DNase I variant is inserted into a replicable vector for further cloning or expression. "Vectors" are plasmids and other DNAs that are capable of replicating within a host cell, and as such, are useful for performing two functions in conjunction with compatible host cells (a vector-host system). One function is to facilitate the cloning of the nucleic acid that encodes a human DNase I variant i.e., to produce usable quantities of the nucleic acid. The other function is to direct the expression of a human DNase I variant. One or both of these functions are performed by the vector in the particular host cell used for cloning or expression. The vectors will contain different components depending upon the function they are to perform

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To produce a human DNase I variant, an expression vector will comprise DNA encoding the variant, as described above, operably linked to a promoter and a ribosome binding site. The variant then is expressed directly in recombinant cell culture, or as a fusion with a heterologous polypeptide, preferably a signal sequence or other polypeptide having a specific cleavage site at the junction between the heterologous polypeptide and the human DNase I variant.

Prokaryotes (e.g., E. coli, and other bacteria) are the preferred host cells for the initial cloning steps of this invention. They are particularly useful for rapid production of large amounts of DNA, for production of single-stranded DNA templates used for site-directed mutagenesis, and for DNA sequencing of the variants generated. Prokaryotic host cells also may be used for expression of DNA encoding a human DNase I variant. Polypeptides that are produced in prokaryotic cells typically will be non-glycosylated.

In addition, the human DNase I variants of this invention may be expressed in eukaryotic host cells, including eukaryotic microbes (e.g., yeast) or cells derived from an animal or other multicellular organism (e.g., Chinese hamster ovary cells, and other mammalian cells), or in live animals (e.g., cows, goats, sheep)

Cloning and expression methodologies are well known in the art. Examples of prokaryotic and eukaryotic host cells, and expression vectors, suitable for use in producing the human DNase I variants of the present invention are, for example, those disclosed in Shak, PCT Patent Publication No. WO 90:07572 (published July 12, 1990).

If prokaryotic cells or cells that contain substantial cell wall constructions are used as hosts, the preferred methods of transfection of the cells with DNA is the calcium treatment method described by Cohen et al., Proc. Natl. Acad. Sci. 69:2110-2114 (1972) or the polyethylene glycol method of Chung et al., Nuc. Acids. Res. 16:3580 (1988). If yeast are used as the host, transfection is generally accomplished using polyethylene glycol, as taught by Hinnen, Proc. Natl. Acad. Sci. U.S.A., 75: 1929-1933 (1978). If mammalian cells are used as host cells, transfection generally is carried out by the calcium phosphate precipitation method. Graham, et al., Virology 52:546 (1978), Gorman, et al., DNA and Protein Eng. Tech. 2:3-10 (1990). However, other known methods for introducing DNA into prokaryotic and eukaryotic cells, such as nuclear injection, electroporation, or protoplast fusion also are suitable for use in this invention.

Particularly useful in this invention are expression vectors that provide for the transient expression in mammalian cells of DNA encoding human DNase I variants. In general, transient expression involves the use of an expression vector that is able to efficiently replicate in a host cell, such that the host cell accumulates many copies of the expression vector and, in turn, synthesizes high levels of a desired polypeptide encoded by the expression vector. Transient expression systems, comprising a suitable expression vector and a host cell, allow for the convenient positive identification of polypeptides encoded by cloned DNAs, as well as for the rapid screening of such polypeptides for desired biological or physiological properties. Wong, et al., Science 228:810-815 (1985); Lee, et al., Proc. Nat Acad. Sci. USA 82:4360-4364 (1985); Yang, et al., Cell 47:3-10 (1986). Thus, transient expression systems are conveniently used for expressing the DNA encoding amino acid sequence variants of native human DNase I, in conjunction with assays to identify those variants that bind actin with lower affinity than native human DNase I as well as assays to measure those variants with DNA-hydrolytic activity

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A human DNase I variant preferably is secreted from the host cell in which it is expressed, in which case the variant is recovered from the culture medium in which the host cells are grown. In that case, it may be desirable to grow the cells in a serum free culture medium, since the absence of serum proteins and other serum components in the medium may facilitate purification of the variant. If it is not secreted, then the human DNase I variant is recovered from lysates of the host cells. When the variant is expressed in a host cell other than one of human origin, the variant will be completely free of proteins of human origin. In any event, it will be necessary to purify the variant from recombinant cell proteins in order to obtain substantially homogeneous preparations of the human DNase I variant. For therapeutic uses, the purified variant preferably will be greater than 99% pure (i.e., any other proteins will comprise less than 1% of the total protein in the purified composition).

Generally, purification of a human DNase I variant is accomplished by taking advantage of the differential physicochemical properties of the variant as compared to the contaminants with which it may be associated. For example, as a first step, the culture medium or host cell lysate is centrifuged to remove particulate cell debris. The human DNase I variant thereafter is purified from contaminant soluble proteins and polypeptides, for example, by ammonium sulfate or ethanol precipitation, gel filtration (molecular exclusion chromatography), ion-exchange chromatography, hydrophobic chromatography, immunoaffinity chromatography (e.g., using a column comprising anti-human DNase I antibodies coupled to Sepharose), tentacle cation exchange chromatography (Frenz, et al., PCT Patent Publication No. WO 93/25670, published December 23, 1993), reverse phase HPLC, and/or gel electrophoresis.

Of course, one skilled in the art will appreciate that the purification methods that are used for native human DNase I may require some modification to be useful in purifying a human DNase I variant, to account for structural and other differences between the native and variant proteins. For example, in some host cells (especially bacterial host cells) the human DNase I variant may be expressed initially in an insoluble, aggregated form (referred to in the art as "refractile bodies" or "inclusion bodies") in which case it will be necessary to solubilize and renature the human DNase I variant in the course of its purification. Methods for solubilizing and renaturing recombinant protein refractile bodies are known in the art (see e.g., Builder, et al., U.S. Patent No. 4,511,502).

In another embodiment of this invention, human DNase I variants are prepared by making covalent modifications directly in a native or variant human DNase I protein. Such modifications are made to affect actin binding or another property of the protein (e.g., stability, biological half-life, immunogenicity), and may be made instead of or in addition to the amino acid sequence substitution, insertion, and deletion mutations described above.

Covalent modifications may be introduced by reacting targeted amino acid residues of the native or variant human DNase I with an organic derivatizing agent that is capable of reacting with selected amino acid side-chains or N- or C-terminal residues. Suitable derivatizing agents and methods are well known in the art.

For example, cysteinyl residues most commonly are reacted with  $\alpha$ -haloacetates (and corresponding amines), such as chloroacetic acid or chloroacetamide, to give carboxymethyl or carboxyamidomethyl derivatives. Cysteinyl residues also are derivatized by reaction with bromotrifluoroacetone,  $\alpha$ -bromo- $\beta$ -(5-

imidozoyl)propionic acid, chloroacetyl phosphate, N-alkylmaleimides, 3-nitro-2-pyridyl disulfide, methyl 2-pyridyl disulfide, p-chloromercuribenzoate, 2-chloromercuri-4-nitrophenol, or chloro-7-nitrobenzo-2-oxa-1,3-diazole.

Histidyl residues are derivatized by reaction with diethylpyrocarbonate at pH 5.5-7.0 because this agent is relatively specific for the histidyl side chain. Para-bromophenacyl bromide also is useful; the reaction is preferably performed in 0.1M sodium cacodylate at pH 6.0.

Lysinyl and amino terminal residues are reacted with succinic or other carboxylic acid anhydrides. Derivatization with these agents has the effect of reversing the charge of the lysinyl residues. Other suitable reagents for derivatizing  $\alpha$ -amino-containing residues include imidoesters such as methyl picolinimidate; pyridoxal phosphate; pyridoxal; chloroborohydride; trinitrobenzenesulfonic acid. O-methylisourea: 2.4-pentanedione; and transaminase-catalyzed reaction with glyoxylate.

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Arginyl residues are modified by reaction with one or several conventional reagents, among them phenylglyoxal, 2,3-butanedione, 1,2-cyclohexanedione, and ninhydrin. Derivatization of arginine residues requires that the reaction be performed in alkaline conditions because of the high pK<sub>4</sub> of the guanidine functional group. Furthermore, these reagents may react with the groups of lysine as well as the arginine epsilon-amino group.

Carboxyl side groups (aspartyl or glutamyl) are selectively modified by reaction with carbodiimides (R'-N=C=N-R'), where R and R' are different alkyl groups, such as 1-cyclohexyl-3-(2-morpholinyl-4-ethyl) carbodiimide or 1-ethyl-3-(4-azonia-4,4-dimethylpentyl) carbodiimide. Furthermore, aspartyl and glutamyl residues are converted to asparaginyl and glutaminyl residues by reaction with ammonium ions.

Covalent coupling of glycosides to amino acid residues of the protein may be used to modify or increase the number or profile of carbohydrate substituents, especially at or adjacent to those residues that are involved in actin binding. Depending on the coupling mode used, the sugar(s) may be attached to (a) arginine and histidine, (b) free carboxyl groups, (c) free sulfhydryl groups such as those of cysteine, (d) free hydroxyl groups such as those of serine, threonine, or hydroxyproline, (e) aromatic residues such as those of phenylalanine, tyrosine, or tryptophan or (f) the amide group of glutamine. Suitable methods are described, for example in PCT Patent Publication No. WO 87/05330 (published September 11, 1987), and in Aplin, et al., CRC Crit. Rev. Biochem., pp. 259-306 (1981).

The covalent attachment of agents such as polyethylene glycol (PEG) or human serum albumin to human DNase I variants may reduce immunogenicity and/or toxicity of the variant and/or prolong its half-life, as has been observed with other proteins. Abuchowski, et al., J. Biol. Chem. 252:3582-3586 (1977); Poznansky, et al., FEBS Letters 239:18-22 (1988); Goodson, et al., Biotechnology 8:343-346 (1990); Katre, J. Immunol. 144:209-213 (1990); Harris, Polyethylene Glycol Chemistry (Plenum Press, 1992). In addition, modification of native human DNase I or a variant thereof by these agents at or adjacent to (i.e., within about five amino acid residues of) an amino acid residue that affects actin binding may result in an actin-resistant variant

In a further embodiment, a human DNase I actin-resistant variant may comprise a mutation at the Asn residue that occurs at position 74 of the native human DNase I amino acid sequence (e.g., a N74D, N74K, or

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N74S mutation), in order to reduce or prevent the deamidation of the DNase I variant. Frenz, et al., PCT Patent Publication No. WO 93/25670, published December 23, 1993. As another example, a human DNase I actin-resistant variant may comprise an amino acid sequence mutation or other covalent modification that reduces the susceptibility of the variant to degradation by proteases (e.g., neutrophil elastase) that may be present in sputum and other biological materials.

The DNA-hydrolytic activity and actin-binding affinity of the human DNase I variants prepared as described above are readily determined using assays and methods known in the art and as described herein. Any such variant having DNA-hydrolytic activity and reduced binding affinity for actin (as defined above) is an actin-resistant variant within the scope of this invention.

The human DNase I actin-resistant variants of this invention are used to reduce the viscoelasticity of DNA-containing material, such as sputum, mucus, or other pulmonary secretions. Such variants are particularly useful for the treatment of patients with pulmonary disease who have abnormal viscous or inspissated secretions and conditions such as acute or chronic bronchial pulmonary disease, including infectious pneumonia, bronchitis or tracheobronchitis, bronchiectasis, cystic fibrosis, asthma, tuberculosis, and fungal infections. For such therapies, a solution or finely divided dry preparation of the actin-resistant variant is instilled in conventional fashion into the airways (e.g., bronchi) or lungs of a patient, for example by aerosolization.

The actin-resistant variants are also useful for adjunctive treatment of abscesses or severe closed-space infections in conditions such as empyema, meningitis, abscess, peritonitis, sinusitis, otitis, periodontitis, pericarditis, pancreatitis, cholelithiasis, endocarditis and septic arthritis, as well as in topical treatments in a variety of inflammatory and infected lesions such as infected lesions of the skin and/or mucosal membranes, surgical wounds, ulcerative lesions and burns. The actin-resistant variant may improve the efficacy of antibiotics used in the treatment of such infections (e.g., gentamicin activity is markedly reduced by reversible binding to intact DNA).

Native human DNase I and actin-resistant variants thereof also may be useful for the treatment for systemic lupus erythematosus (SLE), a life-threatening autoimmune disease characterized by the production of diverse autoantibodies. DNA is a major antigenic component of the immune complexes. In this instance, the human DNase I (native or variant) may be given systemically, for example by intravenous, subcutaneous, intrathecal, or intramuscular administration to the affected patient.

Native human DNase I and actin-resistant variants thereof also may be useful for preventing the new development and/or exacerbation of respiratory infections, such as may occur in patients having cystic fibrosis, chronic bronchitis, asthma, pneumonia, or other pulmonary disease, or patients whose breathing is assisted by ventilator or other mechanical device, or other patients at risk of developing respiratory infections, for example post-surgical patients.

The actin-resistant variants can be formulated according to known methods to prepare therapeutically useful compositions. A preferred therapeutic composition is a solution of an actin-resistant variant in a buffered or unbuffered aqueous solution, and preferably is an isotonic salt solution such as 150 mM sodium chloride containing 1.0 mM calcium chloride at pH 7. These solutions are particularly adaptable for use in

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commercially-available nebulizers including jet nebulizers and ultrasonic nebulizers useful for administration directly into the airways or lungs of an affected patient.

In another embodiment, the therapeutic composition comprises a dry powder of the actin-resistant variant, preferably prepared by spray-drying of a solution of the actin-resistant variant, essentially as described in co-pending U.S. Patent Application Serial No. 08/206,020 (filed March 4, 1994).

In a further embodiment, the therapeutic composition comprises cells actively producing an actinresistant variant of human DNase I. Such cells may be directly introduced into the tissue of a patient, or may
be encapsulated within porous membranes which are then implanted in a patient, in either case providing for
the delivery of the actin-resistant variant into areas within the body of the patient in need of increased
concentrations of DNA-hydrolytic activity. For example, the patient's own cells could be transformed, either
in vivo or ex vivo, with DNA encoding an actin-resistant variant of human DNase I, and then used to produce
the DNase I directly within the patient.

The therapeutically effective amount of an actin-resistant human DNase I variant will depend, for example, upon the amount of DNA and actin in the material to be treated, the therapeutic objectives, the route of administration, and the condition of the patient. Accordingly, it will be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. In view of its reduced binding affinity for actin and consequential increased DNA-hydrolytic activity in the presence of actin relative to native human DNase I, the amount of an actin-resistant variant required to achieve a therapeutic effect may be less than the amount of native human DNase I necessary to achieve the same effect under the same conditions. Generally, the therapeutically effective amount of the actin-resistant variant will be a dosage of from about 0.1 µg to about 5 mg of the variant per kilogram of body weight of the patient, administered within pharmaceutical compositions, as described herein.

An actin-resistant DNase I variant optionally is combined with or administered in concert with one or more other pharmacologic agents used to treat the conditions listed above, such as antibiotics, bronchodilators, anti-inflammatory agents, mucolytics (e.g. n-acetyl-cysteine), actin binding or actin severing proteins (e.g., gelsolin; Matsudaira et al., Cell 54:139-140 (1988); Stossel, et al., PCT Patent Publication No. WO 94/22465 (published October 13, 1994)), protease inhibitors, or gene therapy product (e.g., comprising the cystic fibrosis transmembrane conductance regulator (CFTR) gene, Riordan, et al., Science 245:1066-1073 (1989)).

The following examples are offered by way of illustration only and are not intended to limit the invention in any manner. All patent and literature references cited herein are expressly incorporated.

#### **EXAMPLE 1**

#### Mutagenesis of Human DNase I

E. coli strain CJ236 (BioRad Laboratories, Richmond, California USA) was transformed with plasmid pRK.DNase.3 using the method of Chung et al. (Nuc. Acids. Res. 16:3580 (1988). The plasmid pRK DNase.3 used in making the present invention is as described in PCT Patent Publication No. WO 90/07572 (published July 12, 1990), except that the nucleotide sequence encoding human DNase 1 is as shown in Figure 1. Transformed cells were plated on LB agar plates containing 50 μg/ml carbenicillin and grown overnight at 37°C. 2YT broth (5 ml) containing 50 μg/ml carbenicillin and 10 μl VCSM13 helper phage (Stratagene, La

Jolla, California USA) was inoculated with an individual colony from the agar plate and grown overnight at 37°C with agitation. Single stranded DNA was isolated from this culture and used as template for subsequent mutagenesis.

Site-directed mutagenesis was accomplished using synthetic oligonucleotides according to the method of Kunkel, et al. (Meth. Enzymol. 154: 367-382 (1987). The mutagenic oligonucleotides were 21-mers or 24-mers, having either 9 or 12 exact base matches 5' to the mismatched codon and 9 exact base matches 3' to the mismatched codon. Following mutagenesis, single stranded DNA from individual clones was subjected to dideoxy sequencing (Sanger, et al., Proc. Nat. Acad. Sci. USA 74: 5463-5467 (1977)). DNA having variant nucleotide sequences then was transformed as described above into E. coli strain XL1 Blue MRF' (Stratagene). After plating and single colony isolation as before, individual colonies were used to inoculate 0.5 liter LB broth containing 50 ug/ml carbenicillin. Following growth overnight with agitation at 37° C, the cells were harvested by centrifugation and the variant DNA (in the expression vector) was purified using Qiagen tip-500 columns (Qiagen Inc., Chatsworth, California USA).

Figures 2-6 identify the different human DNase I variants that were made. In the figures and throughout the specification, the description of the amino acid substitution mutation(s) present in a DNase I variant is abbreviated by a first alphabetical letter, a number, and a second alphabetical letter. The first alphabetical letter is the single letter abbreviation of amino acid residue in native (wild-type) human mature DNase I, the number indicates the position of that residue in native human mature DNase I (numbering as shown in Figure 1), and the second alphabetical letter is the single letter abbreviation of the amino acid residue at that position in the variant DNase I. For example, in the DNase I variant having a D53R mutation, the aspartic acid (D) residue at position 53 in native human mature DNase I has been replaced by an arginine (R) residue. Multiple mutations in a single variant are designated similarly, with a colon (:) separating each of the different mutations that are present in the variant. For example, the designation D53R:Y65A indicates that the variant has a D53R mutation and a Y65A mutation.

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#### EXAMPLE 2

#### **Expression of Human DNase J Variants**

Human embryonic kidney 293 cells (ATCC CRL 1573, American Type Culture Collection, Rockville, Maryland USA) were grown in serum containing media in 150 mm plastic Petri dishes. Log phase cells were transiently cotransfected with 22.5 µg purified variant DNA (prepared as described above) and 17 µg adenovirus DNA using the calcium phosphate precipitation method (Gorman, et al., DNA and Protein Eng. Tech. 2.3-10 (1990)). Approximately 16 hours after transfection, the cells were washed with 15 ml phosphate buffered saline and the media was changed to serum free media. Two harvests of the cell culture media were taken from each plate, the first at either 24 or 72 hours and the last at 96 hours following the serum free media change. A total of approximately 50 ml of cell culture supernatant containing the DNase I variant was obtained in this way. The pool of culture supernatant collected from each plate was concentrated 5 to 50 fold using Centriprep 10 concentrators, and the concentrates were assayed to determine various biochemical and biological activities of the DNase I variants.

Concentrate containing native human DNase I was prepared by the same procedure as described above, except that the 293 cells were transiently transfected with plasmid pRK.DNase.3

#### **EXAMPLE 3**

## Biochemical and Biological Activities of Human DNase I Variants

## 5 I. Relative Specific Activity

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The relative specific activity of DNase I variants was assessed by comparing the activity of the variant to that of native human DNase I in two different assays. In particular, the relative specific activity of the variants is defined as the concentration of the variant (in µg/ml) determined in a methyl green activity assay (Sinicropi, et al., Anal. Biochem. 222:351-358 (1994); Kurnick, Arch. Biochem. 29:41-53 (1950)) divided by the concentration of the variant (in µg/ml) determined in a DNase I ELISA assay (described below). In both the methyl green activity assay and the DNase I ELISA assay, the standard curves were determined using Pulmozyme® human DNase I. The relative specific activity of native human DNase I and variants are shown in Figures 2A-D.

The methyl green activity assay (Sinicropi, et al., Anal. Biochem. 222:351-358 (1994); Kurnick, Arch. Biochem. 29:41-53 (1950)) utilizes methyl green dye, which intercalates approximately every 10 bases in the DNA, resulting in a green substrate. As the DNA is cleaved by the DNase I, the methyl green dye is released and oxidized to a colorless form. Thus, the loss of green color is proportional to the amount of DNase I added to the assay sample. The amount of DNase I present in the assay is then quantitated by comparison to a standard curve that is prepared by assaying known quantities of DNase I.

The DNase I ELISA assay involves coating microtiter plates with a goat anti-DNase I polyclonal antibody, adding the sample to be assayed, and detecting any resulting bound DNase I with a rabbit anti-DNase I polyclonal antibody which is conjugated to horseradish peroxidase (HRP). When HRP substrate and color development reagent are added, the color developed is proportional to the amount of DNase I present in the sample. The amount of DNase I present in the assay is then quantitated by comparison to a standard curve that is prepared by assaying known quantities of DNase I.

In both assays, multiple dilutions of the samples were assayed and those values which fell in the midrange of the standard curve were averaged and standard deviations calculated.

Also, the DNase I concentration as determined by the DNase I ELISA assay was used to standardize DNase I concentrations in other assays in which the DNase I variants were characterized (e.g., in assays of inhibition by actin, described below).

## Il Actin Inhibition of DNase I Hydrolytic Activity

G-actin (Kabsch, et al., Ann. Rev. Biophys. Biomol. Struct. 21:49-76 (1992)) was prepared by dialyzing overnight a 1 mg/ml solution of actin (obtained either commercially (Sigma, St. Louis, Missouri USA) or prepared by the method of Pardee, et al., Meth. Enzymol. 85:164-181 (1982)) against 5 mM HEPES, pH 7.2, 0.2 mM CaCl<sub>2</sub>, 0.5 mM ATP, 0.5 mM β-mercaptoethanol at 4°C. After centrifugation at 13,000 x g for 5 min. the amount of G-actin was quantitated by measuring the absorbance at 290 nm; a 1 mg/ml solution has an

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absorbance of 0.66 OD. The amount of G-actin preparation required to substantially (>50% inhibition) but not totally inhibit the DNA-hydrolytic activity of native human DNase I was determined in preliminary experiments under the same conditions used for each assay.

Sensitivity to actin inhibition was assessed by measuring the DNA-hydrolytic activity of the variants in the presence and absence of actin in either of two different assays, the methyl green assay previously described and a hyperchromicity assay which is based on the increase in absorbance at 260 nm upon denaturation and depolymerization of DNA (Kunitz, J. Gen. Physiol. 33:349-362 (1950); Kunitz, J. Gen. Physiol. 33:363-377 (1950)). The percent inhibition of selected variants in these assays are shown in Figures 3 and 4.

In the hyperchromicity assay, concentrated culture supernatants (prepared as described above, containing DNase I variants) were incubated either with no added or a 2- to 3-fold molar excess of actin in buffer A (25 mM HEPES, pH 7.5, 4 mM CaCl<sub>2</sub>, 4 mM MgCl<sub>2</sub>, 0.1% BSA) for one hour at room temperature before being added to a cuvette containing 40 µg DNA in a total assay volume of 1.0 ml. The final concentration of the DNase I variant in the assay was approximately 26 nM, as determined by DNase I ELISA assay. The rates of DNA hydrolysis by the DNase I variants in the presence and absence of actin were measured The percent activity shown in Figures 3 and 4 was calculated by determining the ratio of the DNA hydrolytic activity of the human DNase I (native or variant) in the presence of actin to its DNA-hydrolytic activity in the absence of actin and multiplying by 100.

In the methyl green assay, concentrated culture supernatants (prepared as described above, containing DNase I variants) were incubated either with no added actin or a 1000-fold molar excess of actin in buffer B (25 mM HEPES, pH 7.5, 4 mM CaCl<sub>2</sub>, 4 mM MgCl<sub>2</sub>, 0.1% BSA, 0.01% thimerosal, and 0.05% Tween 20) at 37°C for 16 hours. The concentration of active enzyme in each case was estimated by comparison with the standard curve of Pulmozyme®. The "percent activity" remaining of the variant refers to the 100 times the ratio of the activity in the presence of actin to the activity in the absence of actin.

As shown in Figures 3 and 4, the DNA-hydrolytic activity of native human DNase is substantially reduced in the presence of actin. By comparison, various single- and multiple-residue variants of native human DNase are relatively resistant to inhibition by actin, as indicated by their having greater DNA-hydrolytic activity in the presence of actin than native human DNase I.

### III. Actin Binding ELISA

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A microtiter based assay was developed to measure the binding of native human DNase I and DNase I variants to immobilized actin. First, the wells of a MaxiSorp plate (Nunc, Inc., Naperville, Illinois, USA) were coated with 100 ul per well human GC globulin (Calbiochem, La Jolla, California USA), an actin binding protein (Goldschmidt-Clermont, et al, Biochem, J. 228:471-477 (1985), McLeod, et al., J. Biol. Chem. 264:1260-1267 (1989), Houmeida, et al., Eur. J. Biochem. 203:499-503 (1992)), at a concentration of 10 ug/ml in 25 mM HEPES, 4 mM MgCl<sub>2</sub>, 4 mM CaCl<sub>2</sub>, pH 7.2, at 4°C for 16-24 hours. After discarding the GC globulin, excess reactive sites were blocked by the addition of 200 ul per well buffer C (buffer C is the same as buffer B, above, with the addition of 0.5 mM adenosine triphosphate.

buffer C was used as the assay diluent in all subsequent steps unless otherwise noted) and incubating the plate on a shaker for 1-2 hours at room temperature. Each incubation step which follows was carried out at room temperature for one hour on a Mini Orbital Shaker (Bellco Biotechnology, Vineland, New Jersey USA); between each of the steps, the plate was emptied and washed 6 times with phosphate buffered saline containing 0.05% Tween 20 with a Microwash II plate washer (Skatron A/S, Norway). Next, G-actin, prepared as described above, was diluted to 50 ug/ml in buffer C and 100 ul was added to each well; the plates were incubated and washed, and 100 ul of various dilutions of Pulmozyme® and cell culture media containing either native human DNase I or variants thereof were added to the wells and the plates incubated and washed. Finally, 100 ul of a 1/25,000 dilution of an anti-human DNase I rabbit polyclonal antibodyhorseradish peroxidase conjugate (original stock concentration was 465 ug/ml) was added to each well. After incubation and washing, color development was initiated by the addition of 100 ul per well color development reagent (Sigma Fast o-phenylenediamine and urea/H2O2 tablets solubilized according to the manufacturer's recommendation) and stopped by the addition of 100 ul per well 4.5 N H<sub>2</sub>SO<sub>4</sub>. The absorbance at 492 nm was recorded and plotted versus the concentration of DNase I originally added to the well. Sigmoidal curves resulted for native human DNase I and those variants which bound to actin; these curves were fit to a four parameter equation by nonlinear regression analysis (Marquardt, J. Soc. Indust. Appl. Math. 11:431-441 (1963); the concentration of each DNase I (native or variant) required to give a half-maximal signal in the assay was calculated from the curves and is referred to as the  $EC_{50}$  value. The molecular mass of native human DNase I and the variants was assumed to be 37,000 Daltons.

The relative binding affinity of each human DNase I variant was calculated by dividing the EC<sub>50</sub> value of the variant by the EC<sub>50</sub> value of native human DNase I determined in the ELISA assay, and the results are shown in Figures 5A-D. By way of example, if the relative binding affinity of the human DNase I variant were calculated to be 5, this value would indicate that the EC<sub>50</sub> value of the variant is 5-fold greater than the EC<sub>50</sub> value of native human DNase, or in other words, that the variant has an affinity for actin that is 5-fold less than the affinity of native human DNase I for actin in this ELISA assay.

#### IV. Sputum Compaction Assays

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A sputum compaction assay (PCT Patent Publication No. WO 94/10567, published May 11, 1994) was used to measure the relative viscoelasticity of sputum from cystic fibrosis patients ("CF sputum") before and after incubation with native human DNase I and different DNase I variants. After mixing CF sputum with a DNase I sample and incubating for 20 min at room temperature, the semi-solid solutions were loaded into capillary tubes which then were centrifuged at 12,000 rpm for 20 minutes. Following centrifugation, the height of the pellet was measured and compared to the height of the solution plus pellet. These measurements were then used to calculate the percent compaction of the sputum, which correlates with the viscoelasticity of the sputum

The percent compaction determined upon treatment of CF sputum with native human DNase I and human DNase I actin-resistant variants is shown in Figure 6. These results indicate that the human DNase I

actin-resistant variants are more effective than native human DNase I in reducing the viscoelasticity of CF sputum, as determined by the compaction assay.

### SEQUENCE LISTING

- (1) GENERAL INFORMATION:
  - (i) APPLICANT: Genentech, Inc.
  - (ii) TITLE OF INVENTION: HUMAN DNASE I VARIANTS
- 5 (iii) NUMBER OF SEQUENCES: 98
  - (iv) CORRESPONDENCE ADDRESS:
    - (A) ADDRESSEE: Genentech, Inc
    - (B) STREET: 460 Point San Bruno Blvd
    - (C) CITY: South San Francisco
- 10 (D) STATE: California
  - (E) COUNTRY: USA
  - (F) ZIP: 94080
  - (v) COMPUTER READABLE FORM:
    - (A) MEDIUM TYPE: 3.5 inch, 1.44 Mb floppy disk
- 15 (B) COMPUTER: IBM PC compatible
  - (C) OPERATING SYSTEM: PC-DOS/MS-DOS
  - (D) SOFTWARE: WinPatin (Genentech)
  - (vi) CURRENT APPLICATION DATA:
    - (A) APPLICATION NUMBER:
- 20 (B) FILING DATE:

30

3.5

- (C) CLASSIFICATION:
- (vii) PRIOR APPLICATION DATA:
  - (A) APPLICATION NUMBER: PCT/US95/02366
  - (B) FILING DATE: 02/24/95
- 25 (viii) ATTORNEY/AGENT INFORMATION:
  - (A) NAME: Johnston, Sean A.
  - (B) REGISTRATION NUMBER: 35,910
  - (C) REFERENCE/DOCKET NUMBER: P0925P1PCT1
  - (ix) TELECOMMUNICATION INFORMATION:
  - (A) TELEPHONE: 415/225-3562
    - (B) TELEFAX: 415/952-9881
    - (C) TELEX: 910/371-7168
  - (2) INFORMATION FOR SEQ ID NO:1:
    - (i) SEQUENCE CHARACTERISTICS:
      - (A) LENGTH: 260 amino acids
      - (B) TYPE: Amino Acid
      - (D) TOPOLOGY: Linear
    - (ii) MOLECULE TYPE: Amino Acid
    - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:
- 40 Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys
  1 5 10 15

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	Gl	u Va	ıl Me	t Le	u Ly 26										
	(2)	INE	FORMA	10IT	1 FOF	SEC	) ID	<b>N</b> O : 2	2:						
35			(B)	LENG TYPE TOPG	STH: E: Ar DLOG'	260 nino Y: L:	amir Acid Inean	no ac i	cids						

(xi)	SEQUENCE	DESCRIPTION:	SEQ	ID	NO:2:
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(2) INFORMATION FOR SEQ ID NO:3:

	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 260 amino acids</li><li>(B) TYPE: Amino Acid</li><li>(D) TOPOLOGY Linear</li></ul>													
5		CULE TY		nino A	cid									
	(xi) SEQU	ENCE DE	SCRIPT	: MOI	SEQ	ID NO	):3:							
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**24**5 **25**0 **25**5

Glu Val Met Leu Lys 260

#### (2) INFORMATION FOR SEQ ID NO:4:

- 5 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 260 amino acids
  - (B) TYPE: Aminc Acid(D) TOPOLOGY: Linear
  - (ii) MOLECULE TYPE: Amino Acid
- 10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

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1 5 10 15

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Met Gly Asp Phe Asn Ala Gly Cys Ser Tyr Val Arg Pro Ser Gln 170 175 180

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15	(A) L (B) T	ENCE CHAR ENGTH: 2 YPE: Ami OPOLOGY:	60 amin	TICS: O acids	s			
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- 27 -

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	Түг	Lys	s Glu	a Arg	Tyr 80		Phe	Val	Туг	Arg 85		Asp	Gln	n Val	Ser 90
35	Ala	a Val	Asp	Ser	Tyr 95		Туг	Asp	Asp	100		s Glu	ı Pro	суѕ	Gly 105
	Ası	a Ası	Thr	r Phe	Asn 110		g Glu	Pro	Ala	a Ile 119		L Arg	g Ph€	e Phe	Ser 120

	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130		Pro	Leu	Hıs	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145		Leu	Tyr	Asp	Val 150
5	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160		Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	<b>As</b> n 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
10	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
15	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
20	Glu	Val	Met	Leu	Lys 260										
	(2)	NFO	RMAT:	ION I	FOR S	SEQ :	ID NO	8:0							
25	i )	()	EQUE: A) L! B) T' D) T(	ENGTI PE :	1: 26 <b>A</b> mir	50 ar	mino cid		is						
	(xi	.) SI	EQUE	1CE I	DESCR	RIPT	ION:	SEQ	ID 1	NO : 8	:				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
3 C	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	Asp	<b>Le</b> u <b>4</b> 5
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
15	Asp	Thr	туr	His	Tyr 65	Val	Val	Ser	Glu	Prc 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90

	Ala	Val	Asp	Ser	<b>Tyr</b> 95	Tyr	Tyr	qzA	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
5	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	Hıs	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
1 C	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	lle	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
15	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215		Ala	Gly	Met	<b>Leu</b> 220	Leu	Arg	Gly	Ala	<b>Val</b> 225
20	Val	Pro	Asp	Ser	Ala 230		Pro	Phe	Asn	Phe 235		Ala	Ala	Tyr	Gly 240
	Leu	ser	Asp	Glr	1 Leu 245		Gln	Ala	Ile	Ser 250		His	Tyr	Pro	Val 255
	Glu	ı Val	L Met	Lev	ı Lys 260										
25	(2)	INF	ORMAT	иог	FOR	SEQ	ID N	10 : 9 :							
			(A) I	LENG:		260 a									
30	(:	xi)	SEQUI	ENCE	DES	CRIP'	NOIT	: SE(	Q ID	NO : 9	<b>)</b> :				
		u Ly 1	s Il	e Al		a Pho	e Ası	ı Ile	≘ Glı	n Thi		e Gly	y Glu	Thr	Lys 15
	Ме	t Se	r As:	n Al	a Th 2		u Vai	l Se	r Ty:	r Ile 2!		l Glr	n Ile	e Lei	Ser 30
35	Ar	g Ty	r As	p Il		a Le 5	u Va	l Gl	n Gl	u Val		g Ası	p Sei	г Туз	Leu 45
	Th	r Al	a Va	l Gl		s Le C	u Le	u As	p As	n Le		n Gli	n Ası	p Ala	a Pro

	As	p Th	r Ty:	r Hi:	5 Tyr 65	val	l Va]	. Ser	Glu	Pro 70		ı Gly	/ Arg	AS:	n Se:
	ту	r Ly	s Gli	u Arg	8 Tyr	Leu	ı Ph∈	e Val	Tyr	Arg		Asp	Gln	va:	l Se:
5	Ala	a Va.	As <sub>I</sub>	) Ser	Tyr 95	Туг	Tyr	Asp	Asp	Gly 100		Gl::	Pro	Cys	5 Gly 105
	Ası	n Ası	p Thr	Ph∈	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Ph∈	Ser 120
10	Arg	Phe	e Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	' Asp	Ala 1 <b>4</b> 0	Val	Ala	Glu	Ile	<b>Asp</b>	Ala	Leu	Tyr	Asp	Val
	Tyr	Let	l Asp	Val	Gln 155	Glu	Lys	Trp	Glγ	Leu 160	Glu	Asp	Val	Met	Leu 165
15	Met	Gly	' Asp	Phe	<b>Asn</b> 170	Ala	Gly	Cys	Ser	<b>Tyr</b>	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro	Thr	Phe	Gln	Trp	Leu 195
20	Ile	Pro	qeA	Ser	<b>A</b> la 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
25	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										
	(2)	INFOI	RMATI	ON F	OR S	EQ I	D NO	:10:							
30	( i	( Z		NGTH PE:	HARA I: 26 Amin GY:	0 am 0 Ac	ino id	CS: acid	s						
	(xi	) SE	QUEN	CE D	ESCR	IPTI	ON :	SEQ	ID N	0:10	:				
35	Leu 1	Lys	Ile	Ala	Ala . 5	Phe .	Asn	Ile	Gln :	Thr I	Phe (	Gly (	Glu :	Thr	Lys 15

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25

Met Ser Asn Ala Thr Leu Val Ser Tyr Ile Val Gln Ile Leu Ser

20

	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser '	Trp :	<b>Leu</b> 45
	Thr	Ala	Val	Gly	Lys 50	Гел	Leu	Asp	Asn	Leu 55	Asr.	Gln	Asp .	Ala	Pro 60
5	Asp	Thr	Туг	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Glr.	Val	Ser 90
10	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	y Phe	e Thr	Glu	Val 125		Glu	Phe	Ala	11e	Val	Pro	Leu	His	Ala 135
15	Ala	a Pro	o Gly	Asp	Ala 140		Ala	Glu	ılle	2 Asp	Ala	Leu	Tyr	Asp	Val 150
	ту	r Le	u Asp	Val	. Glr 155		ı Lys	Trp	o Gly	/ Leu 160	Glu	Asp	Val	Met	L <b>e</b> u 165
20	Me	t Gl	y Ası	⊃ Phe	2 Asi		a Gly	, Cy:	s Se	r Tyr 175	val	Arg	Pro	Ser	Gln 180
	Tr	p Se	r Se	r Il	e Arg		u Trj	p Th	r Se	r Pro	Thr	r Ph∈	e Gln	Trp	Leu 195
	Il	e Pr	o As	p Se	r Al.		p Th	r Th	r Al	a <b>Th</b> i	r Pro	o Thi	r His	cys	Ala 210
25	ту	r As	sp Ar	g Il	e Va 21		1 <b>A</b> 1	a Gl	у Ме	t Le <sup>-</sup> 22	u Le	u Arg	g Gly	/ Ala	225
	Va	al Pi	ro As	p Se	r Al 23		u Pr	o Ph	ie As	n Ph 23	e Gl 5	n Al-	a Ala	а Ту	Gly 240
30	L€	eu S	er As	sp Gl	n Le		la Gl	n Al	a Il	.e Se 25	r As O	p Hi	s Ty	r Pr	o Val 255
	G	lu V	al Me	≥t Le	eu Ly 26										
	(2	) IN	FORM	OITA	v FOI	R SE	QID	<b>N</b> O : :	11:						
					- CII	N D N C	TEDI	erre	ς.						

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 260 amino acids
    - (B) TYPE: Amino Acid
    - (D) TOPOLOGY: Linear
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

	-	1			5					10	)				Lys 15
	Met	Se	r Asr	a Ala	Thr 20	Leu	Val	. Ser	Туг	7 Ile 25		Gln	Ile	e Leu	Ser 30
5	Arg	g Tyr	Asp	Ile	Ala 35	Leu	Val	Glr	n Glu	Val		Asp	Ser	His	Leu 45
	Thi	Ala	a Val	Gly	Lys 50	Leu	Leu	Ala	Asn	Leu 55		Gln	Asp	Ala	Pro 60
10	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70		Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Тут 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
15	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
20	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
25	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	<b>Ala</b> 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
30	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 2 <b>4</b> 0
	Leu	Ser	Asp	Gln	Leu . 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	<b>Val</b> 255
35	Glu	Val	Met	Leu .	Lys 260										

- (2) INFORMATION FOR SEQ ID NO:12:
  - (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 260 amino acids

(B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

	1,702	,						_							
5	Leu 1	Lys	Ile	Ala i	Ala I	Phe .	Asn :	Ile	Gln	Thr 10	Phe	Gly (	Glu 7	rhr I	.ys 15
	Met	Ser	Asn	Ala	Thr :	Leu	Val :	Ser	Tyr	Ile 25	Val	Gln	Ile 1	Leu S	Ser 30
10	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser 1	His I	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Lys	Asn	Leu 55	Asn	Gln	Asp .	Ala :	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
15	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	<b>G</b> ly 105
20	Asr.	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	. Thr	Glu	Val	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	Hıs	Ala 135
	a [A	Pro	o Gly	. Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145		Leu	Tyr	Asp	<b>Val</b> 150
25	туз	Le	u Asp	o Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160		Asp	Val	Met	Leu 165
	Met	c Gl	y <b>As</b> j	p Phe	<b>Asn</b>		Gly	Cys	s Ser	Tyr 175	· Val	Arg	Pro	Ser	Gln 180
30	Tr	p Se	r Se	r Ile	Arg		Trp	Thi	c Ser	r Pro		Phe	e Gln	Trp	Leu 195
	Il	e Pr	o As	p Ser	r <b>A</b> la		o Thr	Th:	r Alá	a Thi		o Thr	His	Cys	Ala 210
	ту	r As	p Ar	g Ile	e Val		l Alá	a Gl	у Ме	t Lei 22	u Lev	ı Arg	g Gly	/ Ala	. Val 225
35	Va	l Pr	o As	sp Se	r Ala 230		u Pro	o Ph	e As:	n Ph	e Gla	n Ala	a Ala	а Туг	- Gly 240
	L€	eu Se	er As	sp Gl	n Lei 24		a Gl:	n Al	a Il	e S <b>e</b> 25	r As	p Hi	s Ty:	Pic	Val 255

Glu Val Met Leu Lys 260

5

## (2) INFORMATION FOR SEQ ID NO:13:

(i SEQUENCE CHARACTERISTICS:

(A) LENGTH: 260 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

	(x:	i) SI	EQUE	NCE I	DESCI	RIPT	ION:	SEQ	ID I	NO:1	3 :				
10	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
15	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Arg	Asn	<b>Le</b> u <b>5</b> 5	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
20	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Prc	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	<b>As</b> n 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
25	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
30	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	qeA	Phe	<b>As</b> n 170	Ala	Gly	Суѕ	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
35	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	Hıs	Cys	Ala 210
	туr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225

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	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 2 <b>4</b> 5	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Туг	Pro	Val 255
5	Glu	Val	Met	Leu	Lys 260										
	(2)	NFOF	TAMS	ON F	FOR S	EQ I	D NO	:14:							
10	( )	( <i>I</i>	A) LE 3) TY		I: 26 <b>A</b> mir	0 an			is						
	(x:	i) SI	EQUE	VCE I	DESCH	RIPTI	ION:	SEQ	ID 1	NO:14	<b>l</b> :				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
15	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
20	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Tyr	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
25	Ala	Val	Asp	Ser	<b>T</b> yr 95	Tyr	Tyr	Asp	Asp	Gly 100	Сув	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
30	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	<b>Asp</b> 145	Ala	Leu	Tyr	Asp	<b>Val</b> 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
35	Met	Gly	<b>A</b> sp	Phe	<b>Asn</b> 170		Gly	Cys	Ser	Tyr 175		Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185		Trp	Thr	Ser	Pro 190		Phe	Gln	Trp	<b>Leu</b> 195

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		200	205	Pro Thr His Cys Ala 210
		213	220	Leu Arg Gly Ala Val
5		250	235	Gln Ala Ala Tyr Gly 240
		243	n Ala Ile Ser 250	Asp His Tyr Pro Val 255
10	Glu Val Met Lei	260		
	(2) INFORMATION	FOR SEQ ID 1	NO:15:	
15	(A) LENGT (B) TYPE:	CHARACTERIS: H: 260 amino Amino Acid OGY: Linear	CICS: acids	
	(xi) SEQUENCE	DESCRIPTION:	SEQ ID NO:15	:
				Phe Gly Glu Thr Lys 15
20		20	25	Val Gln Ile Leu Ser 30
		35	40	Arg Asp Ser His Leu 45
		30	5.5	Asn Gln Asp Ala Pro 60
25		0.5	70	eu Gly Arg Asn Ser 75
			85	ro Asp Gln Val Ser 90
30		<i>J J</i>	100	ys Glu Prc Cys Gly 105
	Asn Asp Thr Phe	Asn Arg Glu	Pro Ala Ile V 115	al Arg Phe Phe Ser 120
		123	130	al Pro Leu His Ala 135
35	•	.40	145	la Leu Tyr Asp Val 150
	Tyr Leu Asp Val (	ln Glu Lys 55	Trp Gly Leu Gl 160	u Asp Val Met Leu 165

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	Met	Gly	qeA	Phe	Asn 170	Ala	Gly	у Су	s Se	r T)	/r V 75	al	Arg	Pro	Se	r Gl	.n 80
	Trp	Ser	Ser	Ile	Arg 185	Leu	Tr	p Th	ır Se	er Pi	ro T 90	hr	Phe	Gln	Tr	p Le	eu 95
5	Ile	Pro	Asp	Ser	Ala 200	Asp	Th	r Th	nr Al	la T	hr I	ro	Thr	His	: Су	rs Al 21	la 10
	Tyr	Asp	Arg	Ile	Val 215	Val	. Al	a G	ly M	et L 2	eu I 20	Leu	Arg	Glγ	/ Al	la V	al 25
10	Val	Pro	Asp	Ser	Ala 230		ı Pr	o Pl	he A	sn P 2	he (	3ln	Ala	Ala	а Ту	yr G 2	ly 40
	Leu	Ser	c Asp	Gln	Leu 2 <b>4</b> 5		a Gl	ln A	la I	le S	er . 250	Asp	His	Ту	r P	ro V 2	al 55
	Glu	ı Val	l Met	Leu	1 Lys 260												
15	(2)	INF	orma'	TION	FOR	SEQ	ID	NO:	16:								
		(i)	(B)	ENCE LENG' TYPE TOPO	TH: :	260 ino	ami Aci	no a d	S: ici <b>d</b> s	6							
20	(	xi)	SEQU	ENCE	DES	CRI	PTIO	)N: 5	SEQ	ID N	0:16	5:					
	Le	u Ly 1	/s Il	e Al	a Al	a Pi	ne A	sn	Ile	Gln	Thr 10	Phe	e Gl	у G:	lu 7	rnr	Lys 15
	Me	et Se	er As	in Al		r L	eu V	/al	Ser	Tyr	Ile 25	Va	l Gl	n I	le l	Leu	Ser 30
25	Aı	cg T	yr As	sp Il		.a L 35	eu '	Val	Gln	Glu	Val 40	Ar	g As	p S	er :	His	<b>Leu</b> 45
	Tì	nr A	la V	al G		ys L 50	eu :	Leu	Asp	Asn	Leu 55	As	n Gl	ln A	.sp	Ala	Pro 60
30	A	sp T	hr T	yr H		rg V 65	al '	Val	Ser	Glu	Pro	Le	u G	ly A	rg	Asn	Ser 75
	Т	yr L	ys G	lu A	rg T	yr I 80	Leu	Phe	Val	Tyr	Arg	9 P1	c A	sp (	31n	Val	<b>Se</b> r 90
	A	la V	/al A	sp S	er T	yr ' 95	Tyr	Tyr	Asp	Asp	Gl;	0 0	ys G	lu I	?ro	Cys	Gly 105
35	Ą	Asn )	Asp T	Thr F		.sn .10	Arg	Glu	Pro	Alā	11 11	e V	al A	rg :	Phe	Phe	<b>Ser</b> 120
	Į	Arg	Phe :	Thr (		/al	Arg	Glu	Phe	Ala	a Il 13	e V O	al F	ro	Leu	His	: Ala 135

	Ala I	ro Gl	y Ası	Ala 140	u Val	Ala	Glu	ılle	: Asp	Ala	Leu	Tyr	Asj	P <b>Val</b>
	Tyr I	eu As	p Val	. Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
5	Met G	ly As	p Phe	170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp S	er Se	r Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
10	Ile P	ro Ası	9 Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr A	sp Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val Pi	ro Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
15	Leu Se	er Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu Va	l Met	Leu	Lys 260										
	(2) INF	OR <b>MA</b> T	ION F	OR S	EQ I	D NO	:17:							
20	(i)		NCE C ENGTH YPE: OPOLO	: 26 Amin	0 am 0 Ac	ino id	CS: acid	S						
	( <b>x</b> i)	SEQUE	NCE D	ESCR	IPTI	οи: ,	SEQ	ID <b>N</b> (	0:17:					
25	Leu Ly. 1	s Ile	Ala .	Ala 1	Phe 1	Asn :	Ile	Gln 7	Thr P	he C	Sly C	Slu 7	Thr	Lys 15
	Met Se:	r Asn	Ala '	Thr I 20	ieu t	Jal S	Ser 7	Tyr 1	lle V 25	al G	In I	le I	eu .	Ser 30
30	Arg Tyr	Asp	Ile A	Ala I 35	∟eu V	/al (	Sln (	Glu V	/al A 40	rg A	sp S	er H	ls :	Leu 45
	Thr Ala	a Val	Gly I	∟ys I 50	eu L	Jeu A	A qa	sn L	eu A 55	sn G	ln A	sp A	la I	Pro 60
	Asp Thr	Tyr	His T	rp V 65	al V	al s	er G	lu P	ro L	eu G	ly A	rg A	sn S	Ser 75
35	Tyr Lys	Glu .	Arg T	yr L 80	eu P	he V	al T		rg Pi 85	ro A:	sp G	ln V	al S	er 90
	Ala Val	Asp :	Ser T	yr T 95	yr T	yr A	sp A		lу су 00	/s Gl	lu Pi	ro C		ly os

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	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	11e 115	Val	Arg	Phe	Phe	ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
5	Ala	Prc	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	<b>Asp</b>	Ala	Leu	Tyr	qaA	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
10	Met	Gly	Asp	Phe	<b>As</b> n		Gly	Суз	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg		Trp	Thr	Ser	Pro	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200		Thr	Thr	Ala	Th:	Pro	Thr	His	Cys	Ala 210
15	Туг	Asp	Arg	ı Ile	215		Ala	Gly	/ Met	Let 220	Leu )	ı Arg	g Gly	/ Ala	Val 225
	Va]	l Pro	o Asp	ser	23		ı Pro	Phe	e Asr	23!	e Glr	n Ala	a Ala	а Туг	Gly 240
20	Le	u Se	r Asp	o Glr	n Le		a Gli	n Al	a Ile	25	r Asj	p Hi:	s Ty:	r Pro	255
	Gl	u Va	1 Me	t Le	u Ly 26										
	(2)	INF	ORMA	TION	FOR	SEQ	ID	NO : 1	8:						
25		(i)	(B)	LENG TYPE	TH:	260 ino	ERIS amin Acid near	oac L	: eids						
	+	(xi)	SEQU	JENCE	DES	CRI	4OIT9	I: SE	EQ II	NO:	18:				
30	L€	eu Ly 1	ys Il	e Al	a Al	la Pl	ne As	an Il	le Gl	ın Th	ir Ph	ne Gl	y Gl	tu Th	r Lys 15
	M	et S	er As	sn Al		nr L	eu Va	al S	er T	yr I	le Va 25	al G	ln I	le Le	eu Ser 30
	A	rg T	yr A	sp I	le A	la L 35	eu V	al G	ln G	lu V	al A 40	rg A	sp S	er H	is Leu 45
3 5	т	hr A	la V	al G	ly L	ys L 50	eu L	eu A	.sp A	sn L	eu A 55	sn G	ln A	sp A	la Pro 60
	A	sp 1	hr T	yr H	is T	уr V 65	al A	la S	er G	lu P	ro L 70	eu G	ly A	rg A	sn Ser 75

	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	туr	туг	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
5	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
10	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	<b>Le</b> u 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
15	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
20	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
25	Glu	Val	Met	Leu	Lys 260										
	(2)	INFOR	TAMS	ON F	OR S	SEQ I	ID NO	):19:	:						
30	(:	( Z		ENGTH (PE:	I: 26 Amir	o ar	-		is						
	( <b>x</b> :	i! SE	EQUE	ICE I	ESCF	RIPT	ON:	SEQ	ID 1	NO:19	e :				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr	Phe	Gly	Glu	Thr	Lys 15
35	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45

	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Glu	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
5	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	qeA	Gly 100	Cys	Glu	Pro	Cys	Gly 105
10	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	11e 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	<b>Val</b> 150
15	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	<b>Le</b> u 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
20	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215		Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
25	Val	Pro	Asp	Ser	Ala 230		Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245		Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
30	Glu	Val	Met	Leu	260										
	(2)	INF	RMAT	NOI	FOR	SEQ	ID N	10:20	:						
35	(	(	EQUE (A) L (B) T	ENGT	TH: 2 : Ami	260 a	minc cid								
	( >	(1) S	EQUE	ENCE	DESC	CRIPT	: NOI	SEC	Q ID	<b>N</b> O : 2	0:				

Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys

1 5 10

					20					25	i .				Ser 30
	Arg	, Tyr	Asp	) Ile	Ala 35	Leu	Val	Glr	ı Glu	1 Val 40		Asp	) Ser	Hıs	Leu 45
5	Thr	Ala	val	Gly	Lys 50	Leu	Leu	Asp	Asr	Leu 55		Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Lys	Ser	Glu	Pro 70		Gly	Arg	Asn	S <b>e</b> r 75
10	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	<b>As</b> n 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
15	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	<b>Val</b>
20	Туг	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	<b>As</b> n 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
25	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
30	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala		Gly 2 <b>4</b> 0
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr		Val 255
	Glu	Val	Met		Lys 260										

# 35 (2) INFORMATION FOR SEQ ID NO:21:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 260 amino acids
  - (B) TYPE: Amino Acid
  - (D) TOPOLOGY: Linear

(xi)	SEQUENCE	DESCRIPTION:	SEQ	ID	NO:21:	

	120	, ,						_							
	Leu 1	Lys	Ile	Ala .	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
5	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	туг	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu <b>4</b> 5
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
10	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Lys	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
15	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	. Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130		Pro	Leu	His	Ala 135
20	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145		Leu	Tyr	Asp	Val 150
	Tyr	Let	Asp	Val	Gln 155		Lys	Trp	Gly	Leu 160		Asp	val	Met	Leu 165
25	Met	Gl	y <b>As</b> p	) Phe	Asn 170		Gly	Cys	Ser	Tyr 175		. Arg	J Pro	Ser	Gln 180
	Trp	Se:	r Sei	r Ile	Arg 185		Trp	Thr	s Ser	Pro 190		r Phe	e Glr	Trp	Leu 195
	Ile	e Pr	o Ası	p Ser	Ala 200		Thr	Thi	r Ala	a Thi 209		) Thr	His	s Cys	Ala 210
30	Ty	r As	p Ar	g Ile	215		l Ala	Gly	y Mei	Le:		ı Arg	g Gly	/ Ala	Val 225
	Va	l Pr	o As	p Sei	c Ala 230		a Pro	o Phe	e As:	n Ph		n Ala	a Ala	а Туз	Gly 240
35	Le	u Se	er As	p Gli	n Let 24!		a Glr	n Al	a Il	e Se 25		p Hí:	ѕ Ту	r Pro	o Val 255
	Gl	u Va	al Me	t Le	u Ly:										
						000	7.50		_						

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 260 amino acids

(B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

5	( )	i) S	EQUE	NCE	DESC	RIPT	ION:	SEQ	ID	<b>N</b> O : 2	2:				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10		Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thi 20	Leu	Val	Ser	Tyr	Ile 25		Gln	Ile	Leu	Ser 30
10	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu <b>4</b> 5
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
15			Tyr		65					70					75
			Glu		80					85					90
			Asp		95					100					105
20			Thr		110					115					120
			Thr		125					130					135
25			Gly		140					145					150
			Asp		155					160					165
3.0			Asp		170					175					180
30			Ser		185					190					195
			Asp		200					205					210
35			Arg		215					220					225
			Asp		230					235					240
	Leu	ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	Hıs	Tyr	Pro	Val 255

Glu Val Met Leu Lys 260

5

## (2) INFORMATION FOR SEQ ID NO:23:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 260 amino acids
  - (B) TYPE: Amino Acid
  - (D) TOPOLOGY: Linear

#### (x1) SEQUENCE DESCRIPTION: SEQ ID NO:23:

	(X)	) SE	QUEN	ICE L	DESCR	IPTI	ON:	SEQ	ID N	10 : 23	:				
10	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	Ala	<b>Le</b> u <b>4</b> 5
15	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Arg	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
20	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Туг 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
25	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
30	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Суѕ	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
35	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	Hıs	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225

Val Pro Asp Ser Ala Leu Pro Phe Asn Phe Gln Ala Ala Tyr Gly 230 Leu Ser Asp Gln Leu Ala Gln Ala Ile Ser Asp His Tyr Pro Val 245

5 Glu Val Met Leu Lys 260

- (2) INFORMATION FOR SEQ ID NO:24:
  - (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 260 amino acids

10 (B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:
- Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys

  1 5 10 15
- Met Ser Asn Ala Thr Leu Val Ser Tyr Ile Val Gln Ile Leu Ser 20 25 30
  - Arg Tyr Asp Ile Ala Leu Val Gln Glu Val Arg Asp Ser His Leu
    35 40 45
- Thr Ala Val Gly Lys Leu Leu Arg Asn Leu Asn Gln Asp Ala Pro 20 50 55 60
  - Asp Thr Tyr His Ala Val Val Ser Glu Pro Leu Gly Arg Asn Ser 65 70 75
  - Tyr Lys Glu Arg Tyr Leu Phe Val Tyr Arg Pro Asp Gln Val Ser
- 25 Ala Val Asp Ser Tyr Tyr Tyr Asp Asp Gly Cys Glu Pro Cys Gly
  95 100
  - Asn Asp Thr Phe Asn Arg Glu Pro Ala Ile Val Arg Phe Phe Ser
- Arg Phe Thr Glu Val Arg Glu Phe Ala Ile Val Pro Leu His Ala 30 125 130 135
  - Ala Pro Gly Asp Ala Val Ala Glu Ile Asp Ala Leu Tyr Asp Val
  - Tyr Leu Asp Val Gln Glu Lys Trp Gly Leu Glu Asp Val Met Leu 155 160 165
- Met Gly Asp Phe Asn Ala Gly Cys Ser Tyr Val Arg Pro Ser Gln
  170 175
  - Trp Ser Ser Ile Arg Leu Trp Thr Ser Pro Thr Phe Glr. Trp Leu 185 190 195

	Ile	Pro i	Asp	Ser	Ala 200	Asp	Thr	Thr		Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr i	Asp .	Arg	Ile	Val 215	Val	Ala	Gly		Leu 220	Leu	Arg	Gly	Ala	Val 225
5	Val :	Pro .	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu .	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
10	Glu	Val	Met	Leu	Lys 260										
	(2) I	NFOR	TAM	ON I	FOR S	SEQ I	D NO	0:25	!						
15	(i	(A (B	L) LI	E <b>NGT</b> PE :	CHARA H: 26 Amir DGY:	50 <b>a</b> r 10 <b>A</b> 0	mino cid		is						
	(xi	) SE	QUE	NCE I	DESCI	RIPT	ON:	SEQ	ID N	10:25	5 :				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
20	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Arg	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
25	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Arg	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80		Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
3 C	Ala	Val	Asp	Ser	Tyr 95		Tyr	Asp	Asp	Gly 100		Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110		Glu	Pro	Ala	Ile 115		Arg	g Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125		g Glu	ı Phe	e Ala	11e 130		Pro	) Let	ı His	: Ala 135
35	Ala	Pro	Gly	⁄ Asp	140		Ala	a Glu	ılle	145		Le:	ı Tyr	. Asp	Val 150
	Tyr	Leu	Asp	va:	l Glr 159		ı Lys	5 Trp	o Gly	. Leu 160		. Asj	p Val	l Met	L <b>e</b> u

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		1.0			175	Arg Pro Ser Gln 180
		103			190	Phe Gln Trp Leu 195
5	Ile Pro Asp S	er Ala A 200	sp Thr	Thr Ala	Thr Pro 205	Thr His Cys Ala 210
	Tyr Asp Arg I	le Val Va 215	al Ala (	Gly Met	Leu Leu 220	Arg Gly Ala Val
10	Val Pro Asp S	er Ala Le 230	eu Pro I	Phe Asn	Phe Gln 235	Ala Ala Tyr Gly
	Leu Ser <b>A</b> sp G	ln Leu Al 245	a Gln 🏻	Ala Ile	Ser Asp 250	His Tyr Pro Val
	Glu Val Met L	eu Lys 260				
15	(2) INFORMATION	1 FOR SEQ	ID NO:	26:		
	(A) LENG (B) TYPE	E CHARACT STH: 260 C: Amino DLOGY: Li	amino a Acid	S: cids		
20	(xi) SEQUENCE	DESCRIP	rion: si	EQ ID NO	D:26:	
	Leu Lys Ile Al 1	a Ala Phe 5	e Asn I	le Gln 1	Thr Phe G	Gly Glu Thr Lys 15
	Met Ser Asn Al	a Thr Let 20	ı Val Se	er Tyr 1	lle Val G 25	In Ile Leu Ser 30
25	Arg Tyr Asp Il	e Ala Leu 35	Val Gl	ln Glu V	al Arg A 40	sp Ser Ala Leu 45
	Thr Ala Val Gl	30			55	60
30	Asp Thr Tyr His	65 Ala Val	Val Se	r Glu P	ro Leu G. 70	ly Arg Asn Ser 75
	Tyr Lys Glu Arg	Tyr Leu 80	Phe Va	l Tyr A	rg Pro A: 85	∍p Gln Val Ser 90
	Ala Val Asp Ser	Tyr Tyr 95	Tyr As	p Asp Gi	ly Cys Gl	lu Pro Cys Gly 105
35	Asn Asp Thr Phe	Asn Arg	Glu Pro	O Ala II	le Val Ar L5	g Phe Phe Ser 120
	Arg Phe Thr Glu	Val Arg 125	Glu Phe	e Ala Il	le Val Pr 30	o Leu His Ala 135

	Ala Pro G	ly Asp	Ala \ 140	Jal A	la G	3lu :		Asp 1	Ala	Leu '	Tyr A	;	150
	Tyr Leu A	sp Val	Gln (	Glu L	ys 1	Trp (	Gly	Leu 160	Glu	Asp	Val I	Met 1	Leu 165
5	Met Gly A	sp Phe	Asn .	Ala G	Sly (	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser (	Gln 180
	Trp Ser S	er Ile	Arg	Leu T	ſrp '	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
10	Ile Pro A	sp Ser	Ala 200	Asp 7	Thr '	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr Asp A	Arg Ile	Val 215	Val i	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val Pro A	Asp Ser	Ala 230	Leu :	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
15	Leu Ser i	Asp Glr	Leu 245	Ala	Gln	Ala	Ile	ser 250	Asp	His	Tyr	Pro	Val 255
	Glu Val I	Met Let	Lys 260										
	(2) INFOR	MATION	FOR :	SEQ I	D NO	0:27	:						
20	(A (B	QUENCE () LENG () TYPE () TOPO	TH: 2: : Ami:	60 an	nino cid		ds						
	(xi) SE	QUENCE	DESC	RIPT	: <b>N</b> O	SEQ	ID	NO : 2	7:				
25	Leu Lys 1	Ile Al	a Ala 5		Asn	Ile	Glr	Thr		Gly	/ Glu	Thr	Lys 15
	Met Ser	Asn Al	a Thr		Val	Ser	ту	r Ile 25		. Glr	ılle	Leu	Ser 30
30	Arg Tyr	Asp Il	e Ala		Val	Gl	Gl	u Val		g Ası	Ser	Ala	Leu 45
	Thr Ala	Val Gl	ly Lys		Leu	ı Ası	a As	n Le		n Gl:	n Asp	Ala	Pro 60
	Asp Thr	Tyr H	is Ala		Va]	l Se	r Ar	g Pr 7		u Gl	y Arg	g Ası	. <b>Se</b> r 75
35	Tyr Lys	Glu A	rg Ty: 8		ı Phe	e Va	1 Ту		g Pr 5	o As	p Gl:	n Val	l Ser 90
	Ala Val	Asp S		r Tyr 5	Ty	r As	p As	sp Gl	о У СА	s Gl	u Pr	о Су	s Gly 105

	Asn Asp	Thr Phe	Asn /	Arg Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg Phe	Thr Glu	Val 1	Arg Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
5	Ala Pro	Gly <b>As</b> p	Ala V 140	/al Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr Leu	Asp Val	Gln G 155	Slu Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
10	Met Gly 2	Asp Phe	Asn A	la Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp Ser	Ser Ile	Arg L	eu Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile Pro 1	Asp Ser	Ala A 200	sp Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
15	Tyr Asp A	Arg Ile	Val V 215	al Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val Pro A	Asp Ser	Ala L 230	eu Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
20	Leu Ser A	sp Gln	Leu A 245	la Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu Val M	let Leu	Lys 260									
	(2) INFORM	ATION F	OR SE	QIDNO	28:							
25		LENGTH TYPE: TOPOLO	: 260 Amino	amino Acid		s						
	(xi) SEQ	UENCE D	ESCRI	PTION:	SEQ	ID N	0:28	:				
30	Leu Lys I 1	le Ala	Ala Pi 5	ne Asn	Ile	Gln '	Thr I	Phe	Gly (	Glu '	Thr	Lys 15
	Met Ser A	sn Ala	Thr Le	eu Val	Ser	Tyr	Ile N 25	Val (	Gln :	Ile :	Leu	Ser 30
	Arg Tyr A	sp Ile .	Ala Le 35	eu Val	Gln	Glu V	Val 1 40	Arg I	Asp :	Ser (	Cys	Leu 45
35	Thr Ala V	al Gly :	Lys Le 50	eu Leu	Asp .	Asn I	Leu A 55	Asn (	Gln A	Asp A	Ala	Pro 60
	Asp Thr T	yr His	Tyr Va 65	l Val	Ser (	Glu I	Pro I 70	Leu (	Gly A	Arg A	Asn .	Ser 75

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85

Tyr Lys Glu Arg Tyr Leu Phe Val Tyr Arg Pro Asp Gln Val Ser

80

	Ala	Val	Asp	Ser	Tyr 95	Tyr	туr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
5	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
10	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	<b>As</b> n	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
15	Trp	Ser	Ser	Ile	Arg 185		Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200		Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
20	Tyr	Asp	Arg	Ile	219		Ala	Gly	Met	Leu 220		Arg	Gly	Ala	Val 225
	Val	Pro	o Asp	Ser	230		ı Pro	Phe	e Asr	Phe 235		Ala	Ala	туг	Gly 240
	Lev	ı Se	r Asp	o Gli	1 Le		a Glr	n Ala	a Ile	ser 250		His	з Туг	Pro	255
25	Gli	υ Va	l Me	t Le	ս Ly 26										
	(2)	INF	ORMA'	TION	FOR	SEQ	ID I	NO : 2	9 :						
30		(i)	(B)	LENG TYPE	TΗ: : Απ	260 ino	ERIS amin Acid near	o <b>a</b> c							
	(	xi)	SEQU	ENCE	DES	CRIF	NOIT	: SE	Q ID	NO:	29:				
	Le	u Ly 1	s Il	e Al	a Al	a Ph 5	ne As	n Il	e Gl	n Th		e Gl	y Gl	u Th	r Lys 15
35	Me	et Se	er As	in Al		ır L€ 20	eu Va	ıl S∈	er Ty		e Va 5	l Gl	n 11	e Le	u Ser 30
	Aı	rg T	yr As	sp I		la Le 35	eu Va	al Gl	in Gl		1 Ar	g As	sp S€	er Gl	In Leu 45

Thr Ala Val Gly Lys Leu Leu Asp Asn Leu Asn Gln Asp Ala Pro

					50					55					60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Sei 75
5	Туr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	туг	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
10	Asn	Asp	Thr	Phe	<b>A</b> sn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	<b>Va</b> l
15	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
20	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	<b>Val</b> 225
25	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 2 <b>4</b> 0
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	<b>Val</b> 2 <b>5</b> 5
3 C	Glu	Val	Met	Leu	Lys 260										
	(2) I	NFOR	ITAM	on F	FOR S	EQ I	D NO	:30:							
35	(i	4) E)	QUEN LE TY TO	NGTH PE :	I: 26 Amin	0 am	ino id		ls						
_	(xi		CUEN					SEC	מ חד	ا <b>ن ، ع</b> ام					

Leu Lys Ile Ala Ala Phe Asr. Ile Gln Thr Phe Gly Glu Thr Lys
1 5 10 15

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	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	туr	Ile 25	Val (	Gln	Ile	Leu !	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Cys 45
5	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
10	Tyr	Lys	; Glu	Arg	Туг 80	Leu	Phe	Val	туr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	. Val	Asp	Ser	Tyr 95		Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asr	n Ası	p Thr	Phe	2 Asn		g Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
15	Arg	g Ph	e Thi	c Glu	ı Val		g Glu	ı Phe	e Ala	11e 130	Val	Pro	Leu	His	Ala 135
	Al.	a Pr	o Gl	y Ası	p Ala		l Ala	a Gl	ı Ile	Asp	Ala	Leu	туг	Asp	<b>Val</b> 150
20	ту	r Le	u As	p Va	l Gl:		u Ly	s Tr	p Gly	y Let 160	glu	Asp	va]	. Met	Leu 165
	Me	t Gl	y As	p Ph	e As		a Gl	у Су	s Se	r Ty:	r Val	L Arg	g Pro	Ser	Gln 180
	Tı	πp Se	er Se	r Il	.e Ar		u Tr	p Th	r Se	r Pr	0 <b>Th</b> :	r Ph	e Gl	n Tr	195
25	I	le P	ro As	sp Se	er Al		sp Th	ir Th	ar Al	a Th	r Pr	o Th	r Hi	s Cy:	s Ala 210
	T	yr A	sp A	rg I		al Va 15	al A	La G	Ly <b>M</b> ∈	et Le 22	u Le 0	u Ar	g Gl	y Al	a Val 225
<b>3</b> 0	V	al P	ro A	sp S		la L 30	eu P	ro P	ne As	sn Ph 23	ie Gl 35	n Al	a Al	а Ту	r Gly 240
	L	eu S	er A	sp G		eu A 45	la G	ln A	la I	le Se 25	er As	эр Ні	is Ty	r Pr	o Val 255
	G	ilu V	/al M	let L		ys 60									

- 35 (2) INFORMATION FOR SEQ ID NO:31:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 260 amino acids
    - (B) TYPE: Amino Acid
      (D) TOPOLOGY: Linear

(xi)	SEQUENCE	DESCRIPTION:	SEQ	ID	NO:31:
------	----------	--------------	-----	----	--------

	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr	Phe	Gly	Glu	Thr	Lys 15
5	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	туr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	Hıs	Lys 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
10	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
15	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
20	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	<b>Val</b> 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
25	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
30	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asr.	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
35	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										

<sup>(2)</sup> INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 260 amino acids
- (B) TYPE: Amino Acid
- (D) TOPOLOGY: Linear

5	(x:	i) SI	EQUE	NCE I	DESCI	RIPT	ION:	SEQ	ID 1	NO : 3	2 :				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
10	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Arg 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
15	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
20	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
25	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	туг	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
30					Arg 185					190					195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
35	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255

Glu Val Met Leu Lys 260

## (2) INFORMATION FOR SEQ ID NO:33:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 260 amino acids
  - (B) TYPE: Amino Acid
  - (D) TOPOLOGY: Linear

## (x1) SEQUENCE DESCRIPTION: SEQ ID NO:33

	( :	KI)	SEQU	ENCE	DESC	CRIPT	: NOI	SEÇ	ID	<b>N</b> O : 3	33:				
10	Let	ı Ly	s Il	e Ala	a Ala	Phe	e Asn	Ile	Glr	Thr 10		e Gly	/ Glu	ı Thi	Lys 15
	Met	: Se	r Ası	n Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	· Val	Glr	ı Ile	Let	Ser 30
					35					40					Leu 45
15	Thr	Ala	a Cys	s Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thi	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
20				Arg	80					85					90
	Ala	Val	Asp	Ser	Туг 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
				Phe	110					115					120
25	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	11e 130	Val	Pro	Leu	His	<b>Ala</b> 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	туr	Asp	Val 150
30	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	<b>Asn</b> 170	Ala	Glγ	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	<b>A</b> rg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
35	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val .	Ala	Gly .		Leu 220	Leu	Arg	Gly	Ala	Val 225

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	Val Pro	Asp Se	r Ala 230	Leu	Pro l	Phe A	sn Pl	ne Gl 35	n Al	a Al	а Ту	r Gl 24	lу 10
	Leu Ser	Asp Gl	n Leu 245	Ala	Gln .	Ala 1	lle So	er As 50	p Hi	s Ty	r Pr	o V	al 55
5	Glu Val	Met Le	u Lys 260										
	(2) INFO	RMATION	FOR	SEQ :	ID NO	:34:							
10	(	EQUENCE A) LENG B) TYPE D) TOPG	STH: 2 E: Ami	60 at	mino cid	CS: acid	s						
	(xi) S	EQUENC	E DESC	RIPT	ION:	SEQ	ID NO	D: <b>34</b> :					
	Leu Lys 1	s lle A		a Phe	Asn	Ile	Gln :	Thr P	he G	ly G	lu T	hr 1	Lys 15
15	Met Sei	c Asn A	la Thi		ı Val	Ser	Tyr	Ile V 25	al G	ln I	le L	eu :	Ser 30
	Arg Ty:	r Asp I	le Al		ı Val	Gln	Glu	Val A	Arg A	sp S	Ser F	lis	Leu 45
20	Thr Al	a Lys (		s Let	u Lev	Asp	Asn	Leu A	Asn C	3ln A	Asp A	Ala	Pro 60
	Asp Th	r Tyr I		r Va	l Val	. Ser	Glu	Pro :	Leu (	Gly A	Arg A	Asn	Ser 75
	Tyr Ly	rs Glu		r Le 30	u Phe	e Val	Tyr	Arg 85	Pro .	Asp	Gln	Val	Ser 90
25	Ala Va	al Asp	Ser Ty	yr Ty 95	r Ty	r Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn As	sp Thr	Phe A	sn Ar 10	g Gl	u Pro	o Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
30	Arg P	he Thr	Glu V	al A:	rg Gl	u Ph	e Ala	1le 130	Val	Pro	Leu	Hıs	Ala 135
	Ala P	ro Gly		la V	al Al	a Gl	u Ile	Asp	Ala	Leu	Tyr	Asp	Val 150
	Tyr L	.eu Asp		Gln G	lu Ly	ys Tr	p Gly	y Leu 160	Glu	Asp	Val	Met	Leu 165
3 5	Met C	Bly Asp		Asn A	la G	ly Cy	/s Se	r Tyr 175	Val	Arg	Pro	Sei	r Glr 180
	Trp S	Ser Ser	Ile	Arg I 185	Jeu T	rp T	nr Se	r Pro	Thr	Phe	e Gln	Tr	p Let 19!

	Ile Pr	o Asp	Ser	Ala 200	a Asp	p Th:	r Th	r Al	a Th 20	r Pr 5	o Th	r Hi	s Cy	s Ala 210
	Tyr As	p Arg	, Ile	Val 215	. Va]	l Ala	a Gl	y Me	t Le <sup>.</sup> 22		u Ar	g Gl	y Al	a Val 225
5	Val Pr	o Asp	) Ser	Ala 230	Lei	ı Pro	Phe	e Ası	n Pho 23:		n Ala	a Al	а Ту:	r Gly 240
	Leu Se:	r Asp	Gln	<b>Leu</b> 2 <b>4</b> 5	. Ala	Glr	a Ala	a Ile	250		P Hi	з Ту	r Pro	255
10	Glu Vai	l Met	Leu	Lys 260										
	(2) INFO	DRMAT	ION	FOR	SEQ	ID N	TO:35	5 :						
15		SEQUE (A) L (B) T	ENGTI YPE : OPOLO	H: 2 Ami: OGY:	60 a no A Lin	mino cid ear	aci	.ds						
	(xi) S	EQUE	NCE I	DESC	RIPT	ION:	SEQ	ID	NO:3	5 :				
	Leu Lys 1	: Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10		Gly	Glu	Thr	Lys 15
20	Met Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
	Thr Ala	Val	Cys	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
25	Asp Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
30	Ala Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
<b>3</b> 5	Ala Pro	Gly	Asp .	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr Leu	Asp	Val (	Gln ( 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165

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	Met Gly A	sp Ph	e Asn 2	Ala G	ly Cy	ys Se:	r Tyr 175	Val	Arg	Pro S	Ser G 1	ln 80
	Trp Ser S	Ger Il	e Arg 185	Leu T	rp T	hr Se	r Pro	Thr	Phe	Gln '	Trp L	eu .95
5	Ile Pro A	Asp Se	r Ala 200	Asp T	Thr T	hr Al	a Thi	r Pro	Thr	His	Cys A	Ala 210
	Tyr Asp	Arg Il	e Val 215	Val <i>I</i>	Ala G	ly Me	t Lev 22		Arg	Gly	Ala \	/al 225
10	Val Pro	Asp Se	er Ala 230	Leu l	Pro P	he As	n Ph 23	e Gln 5	Ala	Ala	Tyr (	31 y 24 0
	Leu Ser	Asp Gl	n Leu 245	Ala	Gln A	Ala Il	le Se 25	r Asp 0	His	Tyr	Pro '	Val 255
	Glu Val	Met Le	eu Lys 260									
15	(2) INFOR	OITAM	N FOR	SEQ I	D NO:	: 36 :						
	( <i>I</i>	A) LEN	E CHAR GTH: 2 E: Ami OLOGY:	60 am no Ac	nino a							
20	(xi) SI	EQUENC	E DESC	RIPTI	ON:	SEQ I	D NO	: 36 :				
	Leu Lys 1	Ile A	la Ala		Asn	Ile G	ln T	hr Pho	e Gly	/ Glu	Thr	Lys 15
	Met Ser	Asn A	la Thr 20		Val	Ser T	yr I	le Va 25	l Gli	n Ile	Leu	Ser 30
25	Arg Tyr	<b>.</b>										30
	<b>J</b> -	Asp .	(le Ala 39		Val	Gln (	Glu V	al Ar 40	g As	p Ser	His	
	Thr Ala		3 5	Leu				40				Leu 45
30		. Val :	39 Ile Lys 50	s Leu D r Val	Leu	Asp /	Asn L	40 eu As 55	n Gl	n Asp	o Ala	Leu 45 Pro 60
30	Thr Ala	. Val :	39 Ile Lys 5 His Ty 6	E Leu T Val E Leu	Leu Val	Asp /	Asn L Glu F	40 eu As 55 Pro Le 70	n Gl eu Gl	n Asp	o Ala g Asn	Leu 45 Pro 60 Ser 75
30	Thr Ala	Val :	35 Ile Ly: 51 His Ty 6 Arg Ty 8	s Leu Cr Val 5 r Leu	Leu Val	Asp	Asn L Glu F Tyr A	eu As 55 Pro Le 70 Arg Pr	n Gl eu Gl	n Asp y Arg	o Ala g Asn n Val	Leu 45 Pro 60 Ser 75 Ser 90
<b>3</b> 0	Thr Ala	Val : Tyr : s Glu	35 Ile Lys 51 His Ty 6 Arg Ty 8 Ser Ty	E Leu  T Val  Leu  T Leu  T Tyr  T Tyr	Leu Val Phe	Asp Asp	Asn L Glu F Tyr A Asp (	40 As 55 Le 70 Le 85 Sly C	n Gl eu Gl co As	n Asp y Arg ip Gli	o Ala g Asn n Val	Leu 45 Pro 60 Ser 75 Ser 90 Gly 105

	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	<b>Val</b> 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
5	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Prc	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	<b>Le</b> u 195
10	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	Hıs	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
15	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										
	(2) I	NFO	TAMS	ON I	FOR S	SEO :	ID NO	0:37	•						
						-									
20		) SI	EQUEN A) LE B) TY	NCE (	CHARA 1: 26 Amir	ACTEI 50 ar no Ac	RIST: mino cid								
20	(i	) SI (1	EQUEN A) LE B) TY	NCE ( ENGTH (PE:	CHARA H: 26 Amir DGY:	ACTEI 50 ar no Ac Line	RIST: mino cid ear	ICS:	ds	<b>1</b> 0 : <b>3</b> °	7:				
20	(i	) SI (J (I (I	EQUEN A) LE B) TY D) TO	NCE ( ENGTH (PE: DPOL(	CHARA H: 26 Amin DGY:	ACTEI 50 ar no Ac Line	RIST: mino cid car	ICS: acid	ds ID 1			Gly	Glu	Thr	Lys 15
	(i (xi Leu	) SI (I (I ) SI Lys	EQUENCE OF TO	NCE ( ENGTH (PE: DPOLO NCE I	CHARA H: 26 Amir DGY: DESCI Ala 5	ACTEI 50 am no Ac Line RIPT:	RIST: mino cid ear ION:	ICS: acid SEQ	is ID: Gln	Thr 10	Phe				15
	(xi Leu 1	) SI (I (I ) SI Lys	EQUEN A) LE B) TY EQUEN Ile Asn	NCE (PENGTH) POPOLO NCE I Ala	CHARMED AMINOGY: DESCRIPTION Ala 5 Thr 20	ACTEI 50 am no Ao Line RIPT: Phe	RIST: mino cid ear ION: Asn Val	SEQ Ile	is ID i Gln Tyr	Thr 10 Ile 25	Phe Val	Gln	Ile	Leu	15 Ser 30
25	(xi Leu 1 Met	) SI (I (I ) SI Lys Ser	EQUENCY LIE	NCE ( ENGTH YPE: OPOLO NCE I Ala Ala Ile	CHARI H: 26 Amir OGY: DESCI Ala 5 Thr 20 Ala 35	ACTEI 50 and Line RIPT: Phe Leu	RIST: mino cid car ION: Asn Val	SEQ Ile	ID 1 Gln Tyr Glu	Thr 10 Ile 25 Val 40	Phe Val Arg	Gln	Ile Ser	Leu Hıs	15 Ser 30 Leu 45
25	(xi Leu 1 Met Arg	) SE (J) (I) (I) (II) SE Lys Ser Tyr	EQUENCY LIE	NCE (ENGTHYPE: DPOLO NCE I Ala Ala Ile	CHARZE H: 26 Amir DGY: DESCI Ala 5 Thr 20 Ala 35 Lys 50	ACTEI 50 and Action Act	RIST: nino cid car ION: Asn Val Val	ICS: acid SEQ Ile Ser	ID 1 Gln Tyr Glu Asn	Thr 10 Ile 25 Val 40 Leu 55	Phe Val Arg Asn	Gln Asp Glr.	Ile Ser Asp	Leu Hıs Ala	15 Ser 30 Leu 45 Pro 60
25	(xi Leu 1 Met Arg Thr	) SE (X) (II) SE Lys Ser Tyr Ala	EQUENCY LIE	NCE (ENGTHYPE: DPOLO NCE I Ala Ala Ile Lys His	CHARZE H: 26 Amir DGY: DESCI Ala 5 Thr 20 Ala 35 Lys 50 Tyr 65	ACTEI 50 and Action Act	RIST: mino cid car ION: Asn Val Val Leu Val	ICS: acid SEQ Ile Ser Gln	ID : Gln Tyr Glu Asn Glu	Thr 10 Ile 25 Val 40 Leu 55 Pro 70	Phe Val Arg Asn	Gln Asp Glr.	Ile Ser Asp	Leu Hıs Ala Asn	15 Ser 30 Leu 45 Pro 60 Ser 75

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	Asn A	qeA	Thr	Phe	<b>As</b> n	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120	)
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135	<b>a</b> 5
5	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Va:	1 0
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gl <sub>y</sub>	/ Leu 160	Glu	Asp	Val	Met	Le 16	u 5
10	Met	Gly	Asp	Phe	Asn 170		Gly	Cys	s Ser	r Tyr 175	Val	Arg	Pro	Ser	Gl 18	n 0
	Trp	Ser	Ser	Ile	e Arg		Trp	o Thi	s Se	r Pro	o Th:	r Phe	e Gli	n Tr	19	:u 15
	Ile	Pro	Asp	Sei	Ala 200		Th:	r Thi	r Al	a Thi	r Pr	o Th	r Hi	s Су:	s Al	La LO
15	Tyr	Ası	Arg	, Ile	e Vai		l Al	a Gl	у Ме	t Le	u Le O	u Ar	g Gl	y Al	a Va 22	al 25
	Val	Pro	o Ası	e Se	r Al		u Pr	o Ph	e As	n Ph 23	e Gl 5	n Al	a Al	а Ту	r G	ly 40
20	Leu	ı Se	r As	p Gl	n Le 24		a Gl	n Al	a Il	le Se 25	r As	sp Hi	s Ту	r Pr	o V 2	al 55
	Gli	ı Va	l Me	t Le	u Ly 26											
	(2)	INF	ORMA	101T	1 FOF	SEC	) ID	NO:	38:							
25		(i)	(A) (B)	LENG	E CHA ETH: E: An OLOG	260 nino	ami Aci	no a d	S: cids							
	(	xi)	SEQ	JENC	E DE	SCRI	PTIO	N: S	EQ I	.D <b>N</b> O	:38:					
30	Le	u L	ys I	le A	la A	la P 5	he A	sn I	le C	3ln T	hr F	he G	ly G	lu T	hr '	Lys 15
	Me	et S	er A	sn A	la T	hr L 20	eu V	al S	Ser :	ryr I	le \ 25	/al G	iln I	le I	.eu	Ser 30
	A	rg T	yr A	.sp I	le A	la I 35	⊿eu \	/al (	3ln (	Glu V	Val 4	Arg A	Asp S	Ser 1	lis	Leu 45
35	τ	hr A	Ala V	/al /	Arg I	ys 1	Leu 1	Leu l	Asp	Asn l	Leu . 55	Asn (	3ln .	Asp /	Ala	Pro 60
	A	sp :	Thr T	ryr 1	Hıs '	ryr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75

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	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
5	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
10	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	<b>Asn</b> 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
15	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
20	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	<b>Val</b> 255
25	Glu	Val	Met	Leu	Lys 260										
	(2)	INFO	RMAT:	ION !	FOR :	SEQ :	ID N	O:39	:						
30	(:	()			H: 20 Amii	60 <b>a</b> t	mino cid		ds						
	(×.	i) S	EQUE	NCE :	DESC:	RIPT	ION:	SEÇ	ID I	10:3	9 :				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
35	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	<b>Le</b> u <b>4</b> 5

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	Thr	Ala	Val	Tyr	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
5	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
10	Asn	Asp	Thr	Phe	<b>As</b> n 110	Arg	Glu	Pro	Ala	11e 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	<b>Val</b> 150
15	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	<b>Le</b> u 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
20	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	qaA	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215		Ala	Gly	Met	Leu 220		Arg	Gly	Ala	Val 225
25	Val	Pro	Asp	Ser	Ala 230		Pro	Phe	Asn	Phe 235		Ala	Ala	Tyr	Gly 240
	Leu	ser	Asp	Gln	Leu 245		Gln	Ala	Ile	Ser 250		His	Tyr	Pro	<b>Val</b> 255
30	Glu	ı Val	. Met	Leu	Lys 260										
	(2)	INF	ORMAT	NOI	FOR	SEQ	ID N	<b>1</b> 0 : <b>4</b> 0	):						
	,		SEQUE (A) I (B) T	ENGT	TH: 2	260 a	mino								
35			(D) T	COPOL	JOGY :	Lir	near			N.C					
	( 2	xi) :	SEQUE	ENCE	DESC	CRIP?	LICN	: SE(	QI Ç	NO:4	• O :				

Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys 1 5 10 10

					20					25	5				Ser 30
	Arg	у Тул	r Asp	lle	Ala 35	Leu	Val	Gln	Glu	u Val 40		Asp	Ser	His	Leu 45
5	Thi	Ala	a Val	Gly	Lys 50	Leu	Cys	Asp	Ası	Leu 55		Gln	Asp	Ala	Pro 60
	Asp	) Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70		Gly	Arg	Asn	Ser 75
10	Туг	Lys	Glu	Arg	Tyr 80	Leu	Phe	Va]	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
15	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
20	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
25	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
30	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu . 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr		Val 255
	Glu	Val	Met		Lys 260										

# 35 (2) INFORMATION FOR SEQ ID NO:41:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 260 amino acids
  - (B) TYPE: Amino Acid
  - (D) TOPOLOGY: Linear

	(XI	) SE	COFF	ICE D	ESCR.	IPII	ON:	3EQ	10 14	O. <b>4</b> 1	•				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
5	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Lys	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
10	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Туг 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
15	Ala	Val	Asp	Ser	Туг 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	. Thr	Glu	Val 125	Arg	Glu	Phe	Ala	11e		Pro	Leu	His	Ala 135
20	Ala	Pro	Gly	/ Asp	Ala 140	Val	Ala	Glu	Ile	145		Leu	Туг	Asp	Val 150
	Tyr	Le	Asp	o Val	. Gln 155		Lys	Trp	Gly	/ Let		Asp	Val	Met	Leu 165
25	Met	Gl	y Ası	Phe	2 Asn 170		a Gly	Cys	s Sei	Ty:		. Arg	g Pro	Ser	Gln 180
	Tr	e Se	r Se	r Ile	e Arg		ı Trp	Th:	s Se	190		Phe	e Glr	n Trp	195
	Ile	e Pr	o As	p Se:	r Ala 200		7 Thr	Th	r Ala	a Th:		o Thi	r Hi	s Cys	210
30	Ty:	r As	p Ar	g Il	e Val		l Ala	a Gl	у Ме	t Le 22		u Arg	g Gl	y Ala	a Val 225
	Va	l Pr	o As	p Se	r Ala 230		u Pro	o Ph	e As	n Ph 23		n Al	a Al	а Ту	r Gly 240
35	Le	u Se	er As	p Gl	n Le		a Gl:	n Al	a Il	e Se 25		p Hi	s Ty	r Pr	o Val 255
	Gl	.u. Vá	al Me	et Le	u Ly 26										

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 260 amino acids

(B) TYPE: Amino Acid(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42: Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys 10 Met Ser Asn Ala Thr Leu Val Ser Tyr Ile Val Gln Ile Leu Ser Arg Tyr Asp Ile Ala Leu Val Gln Glu Val Arg Asp Ser His Leu 10 Thr Ala Val Gly Lys Leu Met Asp Asn Leu Asn Gln Asp Ala Pro Asp Thr Tyr His Tyr Val Val Ser Glu Pro Leu Gly Arg Asn Ser 15 Tyr Lys Glu Arg Tyr Leu Phe Val Tyr Arg Pro Asp Gln Val Ser Ala Val Asp Ser Tyr Tyr Tyr Asp Asp Gly Cys Glu Pro Cys Gly 100 20 Asn Asp Thr Phe Asn Arg Glu Pro Ala Ile Val Arg Phe Phe Ser 115 Arg Phe Thr Glu Val Arg Glu Phe Ala Ile Val Pro Leu His Ala Ala Pro Gly Asp Ala Val Ala Glu Ile Asp Ala Leu Tyr Asp Val 25 140 Tyr Leu Asp Val Gln Glu Lys Trp Gly Leu Glu Asp Val Met Leu Met Gly Asp Phe Asn Ala Gly Cys Ser Tyr Val Arg Pro Ser Gln Trp Ser Ser Ile Arg Leu Trp Thr Ser Pro Thr Phe Gln Trp Leu 30 185 190 Ile Pro Asp Ser Ala Asp Thr Thr Ala Thr Pro Thr His Cys Ala 200 205 Tyr Asp Arg Ile Val Val Ala Gly Met Leu Leu Arg Gly Ala Val 35 215 Val Pro Asp Ser Ala Leu Pro Phe Asn Phe Gln Ala Ala Tyr Gly 230 235 Leu Ser Asp Gln Leu Ala Gln Ala Ile Ser Asp His Tyr Pro Val 245 250

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Glu Val Met Leu Lys 260

5

## (2) INFORMATION FOR SEQ ID NO:43:

(i)	SEQUENCE	CHARACTERISTICS	;
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- (A) LENGTH: 260 amino acids
- (B) TYPE: Amino Acid
- (D) TOPOLOGY: Linear

# (xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

	(xi	) SI	EQUEN	ICE D	ESCR	IPTI	ON:	SEQ	ID N	0:43	:				
10	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu '	Thr 1	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu <b>4</b> 5
15	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Cys	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
20	Tyr	Lys	s Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	. Val	l Asp	ser	Tyr 95		Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asr	n Asj	p Thi	c Phe	Asn 110		g Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
25	Arg	g Ph	e Thi	r Glu	val 125		g Glu	Phe	e Ala	lle 130	Val	Pro	Leu	Hıs	Ala 135
	Ala	a Pr	o Gl	y Asp	Ala 140		l Ala	Glu	ı Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
30	ту	r Le	u <b>A</b> s	p Vai	l Glr 15		u Lys	5 Trp	p Gly	y Let 160	ı Glu	ı Asp	Val	Met	Leu 165
	Ме	t Gl	y As	p Ph	e As:		a Gly	у Су	s Se	r Tyr 175	r Val	l Arg	g Pro	ser	Gln 180
	Tr	p Se	er Se	er Il	e Ar 18		u Tr	p Th	r Se	r Pro	o Thi	r Ph	e Glr	Trp	195
35	Il	.e P	ro As	sp Se	r Al 20		p Th	r Th	r Al	a Th	r Pr	o Th	r His	s Cys	210
	Τ	/r A	sp Ai	rg Il	e Va. 21		al Al	a Gl	у Ме	t Le 22	u Le O	u Ar	g Gl	y Ala	a Val 225

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Val Pro Asp Ser Ala Leu Pro Phe Asn Phe Gln Ala Ala Tyr Gly Leu Ser Asp Gln Leu Ala Gln Ala Ile Ser Asp His Tyr Pro Val Glu Val Met Leu Lys (2) INFORMATION FOR SEQ ID NO:44: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 260 amino acids (B) TYPE: Amino Acid 10 (D) TOPOLOGY: Linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:44: Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys Met Ser Asn Ala Thr Leu Val Ser Tyr Ile Val Gln Ile Leu Ser 15 Arg Tyr Asp Ile Ala Leu Val Gln Glu Val Arg Asp Ser His Leu Thr Ala Val Gly Lys Leu Leu Asn Leu Asn Gln Asp Ala Pro 20 Asp Thr Tyr His Tyr Val Val Ser Glu Pro Leu Gly Arg Asn Ser Tyr Lys Glu Arg Tyr Leu Phe Val Tyr Arg Pro Asp Gln Val Ser Ala Val Asp Ser Tyr Tyr Tyr Asp Asp Gly Cys Glu Pro Cys Gly 25 Asn Asp Thr Phe Asn Arg Glu Pro Ala Ile Val Arg Phe Phe Ser Arg Phe Thr Glu Val Arg Glu Phe Ala Ile Val Pro Leu His Ala 30 Ala Pro Gly Asp Ala Val Ala Glu Ile Asp Ala Leu Tyr Asp Val 145 Tyr Leu Asp Val Gln Glu Lys Trp Gly Leu Glu Asp Val Met Leu Met Gly Asp Phe Asn Ala Gly Cys Ser Tyr Val Arg Pro Ser Gln 35 175 Trp Ser Ser Ile Arg Leu Trp Thr Ser Pro Thr Phe Gln Trp Leu 190

Ile Pro Asp Ser Ala Asp Thr Thr Ala Thr Pro Thr His Cys Ala Tyr Asp Arg Ile Val Val Ala Gly Met Leu Leu Arg Gly Ala Val Val Pro Asp Ser Ala Leu Pro Phe Asn Phe Gln Ala Ala Tyr Gly 235 Leu Ser Asp Gln Leu Ala Gln Ala Ile Ser Asp His Tyr Pro Val Glu Val Met Leu Lys 10 (2) INFORMATION FOR SEQ ID NO:45: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 260 amino acids (B) TYPE: Amino Acid 15 (D) TOPOLOGY: Linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:45: Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys Met Ser Asn Ala Thr Leu Val Ser Tyr Ile Val Gln Ile Leu Ser 20 Arg Tyr Asp Ile Ala Leu Val Gln Glu Val Arg Asp Ser His Leu 40 Thr Ala Val Gly Lys Leu Leu Met Asn Leu Asn Gln Asp Ala Pro Asp Thr Tyr His Tyr Val Val Ser Glu Pro Leu Gly Arg Asn Ser 25 65 Tyr Lys Glu Arg Tyr Leu Phe Val Tyr Arg Pro Asp Gln Val Ser Ala Val Asp Ser Tyr Tyr Tyr Asp Asp Gly Cys Glu Pro Cys Gly 30 100 Asn Asp Thr Phe Asn Arg Glu Pro Ala Ile Val Arg Phe Phe Ser Arg Phe Thr Glu Val Arg Glu Phe Ala Ile Val Pro Leu His Ala 130 35 Ala Pro Gly Asp Ala Val Ala Glu Ile Asp Ala Leu Tyr Asp Val 140 Tyr Leu Asp Val Gln Glu Lys Trp Gly Leu Glu Asp Val Met Leu 16C

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	Met	Gly	Asp	Phe	<b>Asn</b> 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
5	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	Hıs	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
10	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	туr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										
15	(2)	INFO	RMAT:	ION 1	FOR S	EQ :	ID N	0:46	:						
	(	(. (:		ENGTI YPE :		50 ar 10 Ad	mino cid		ds						
20	( <b>x</b>	i) S	EQUE	NCE I	DESC	RIPT	: NO	SEQ	ID I	NO : 4	5 :				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
25	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Cys	Gln	Asp	Ala	Pro 60
30	Asp	Thr	Tyr	Hıs	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Туr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
35	Asn	Asp	Thr	Phe	<b>As</b> n 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Prc	Leu	His	Ala 135

	Ala	Pro	Gly	Asp	Ala 140	Val .	Ala	Glu	Ile	<b>Asp</b> 145	Ala	Leu	Tyr		Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val		<b>Le</b> u 165
5	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
10	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
15	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	. Val	l Met	. Leu	Lys 260										
	(2)	INF	ORMA?	NOIT	FOR S	SEQ	ID N	0:47	:						
20	(		(A) I	LENGT	CHAR TH: 2: Ami: LOGY:	60 a	mino cid								
	()	ci)	SEQU	ENCE	DESC	RIPT	ION:	SEC	OID	NO:4	7:				
25		LY	s Il	e Ala	a Ala 5	Phe	Asn	Ile	e Glr	Thr		e Gly	/ Glu	Thr	Lys 15
	Met	: Se	r As	n Ala	a Thr 20		Val	Sei	туі	r Ile 25		Glr	ılle	Leu	Ser 30
3 C	Arg	д Ту	r As	p Il	e Ala 35		ı Val	. Gli	n Glv	ı Val		g Asp	ser	His	<b>Le</b> u <b>4</b> 5
	Th	r Al	.a. Va	l Gl	y <b>Lys</b> 50		ı Lev	ı Ası	p Ası	n Lei 59		e Glr	n Asp	Ala	Pro 60
	As	p Th	ir Ty	r Hi	s Tyr 65		l Vai	l Se	r Gl	u Pro		u Gl	y Arg	g Asn	Ser 75
35	Ту	r Ly	ys Gl	u Ar	g Ty1		ı Ph	e Va	1 Ту	r Ar		o As	p Gli	n Val	. Ser 90
	Al	a Va	al As	sp Se	r Ty:		r Ty	r As	p As	p Gl 10		s Gl	u Pr	o Cys	Gly 105

	leA	n As	p Thi	r Phe	Asn 110	Arg	Glu	Pro	Ala	11e	Val	Arg	Phe	Phe	Ser 120
	Arg	g Ph	e Thi	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
5	Ala	Pr	o Gly	/ Asp	Ala 140	Val	Ala	Glu	Ile	Asp	Ala	Leu	Tyr	Asp	Val 150
	Туг	Le	u Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
10	Met	Gl	y Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Se	r Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	Hıs	Cys	Ala 210
15	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
20	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										
	(2)	INFO	RMAT	ION F	OR S	EQ I	D NO	:48:							
25	( =	(	EQUENA) LE B) TY D) TO	ENGTH (PE:	: 26 Amin	0 am	ino	CS: acid	ls						
	(xi	.) s	EQUEN	ICE D	ESCR	IPTI	ON:	SEQ	ID N	O:48	:				
30	Leu 1	Lys	Ile	Ala	Ala 1 5	Phe	Asn	Ile	Gln	Thr	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala '	Thr 1	Leu '	Val :	Ser	Tyr	Ile ' 25	Val	Gln	Ile :	Leu	Ser 30
	Arg	Tyr	Asp	Ile /	Ala I 35	beu '	Val (	Gln (	Glu	Val 1	Arg .	Asp :	Ser 1	His :	Leu 45
35	Thr	Ala	Val	Gly I	-ys I 50	Jeu 1	Leu A	Asp 1	Asn :	Leu I 55	iys (	Gln 2	Asp A	Ala 1	Prc 60
	Asp	Thr	Tyr	His T	Cyr V	al v	Val S	Ser (	Glu 1	Pro I	Leu (	Gly A	Arg A	Asn S	Ser

65

	Tyr Lys Gl	u Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala Val As	p Ser	Туr 95	Tyr	Tyr	qzA	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
5	Asn Asp Th	r Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg Phe Th	r Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
10	Ala Pro Gl	y Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr Leu As	sp Val	Gln 155		Lys	Trp	Gly	Leu 160		Asp	Val	Met	Leu 165
	Met Gly As	sp Phe	<b>Asn</b>		Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
15	Trp Ser S	er Ile	Arg		Trp	Thr	Ser	Pro 190		Phe	Gln	Trp	Leu 195
	Ile Pro A	sp Ser	Ala 200		Thr	Thi	: Ala	205		Thr	His	: Cys	Ala 210
20	Tyr Asp A	rg Ile	Val		Ala	Gly	/ Met	220	ı Leu O	ı Arg	g Gly	/ Ala	Val 225
	Val Pro A	sp Sei	Ala 230		ı Pro	Phe	e Ası	n Pho 23		n Ala	a Ala	а Туг	Gly 240
	Leu Ser A	sp Gli	n Le		a Glr	n Al	a Il	e Se 25	r Ası	p His	з Ту	r Pro	o Val 255
25	Glu Val N	iet Le	u Ly 26										
	(2) INFOR	MOITAN	FOR	SEQ	ID	NO : 4	9:						
30	(i) SE( (A (B (D		TΗ: : Απ	260 ino	amin	o <b>a</b> c	: :ids						
	(xi) SE	QUENCE	DES	SCRIE	TION	: SE	EQ II	ON C	:49:				
	Leu Lys 1	Ile Al	a Al	la Ph 5	ne As	in Il	le G		nr Ph	ie Gl	y Gl	u Th	nr Lys 15
35	Met Ser	Asn Al		<b>hr L</b> e 20	eu Va	al S	er T	yr I	le Va 25	al Gl	ın II	le Le	eu Ser 30
	Arg Tyr	Asp I		la Lo	eu Va	al G	ln G		al Ai	rg A	sp Se	er H	is Leu 45

	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Arg	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
5	Туr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
10	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	<b>Val</b> 150
L 5	туr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	<b>Leu</b> 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Суѕ	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
20	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
25	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
30	Glu	Val	Met	Leu	Lys 260										
	(2)	INFO	RMAT	ION :	FOR	SEQ	ID N	0:50	:						

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH 260 amino acids
  - (B) TYPE: Amino Acid
- 35 (D) TOPOLOGY: Linear
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys
1 5 10 15

	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
5	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Trp	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
L 0	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
15	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
20	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	<b>Asn</b> 170	Ala	Gly	Càa	Ser	<b>Tyr</b> 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
25	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
30	Val	Pro	Asp	ser	Ala 230		Pro	Phe	Asn	Phe 235		Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245		Gln	Ala	Ile	Ser 250	_	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										

## 35 (2) INFORMATION FOR SEQ ID NO:51:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 260 amino acids
  - (B) TYPE: Amino Acid
  - (D) TOPOLOGY: Linear

(xi)	SEQUENCE	DESCRIPTION:	SEO	ID	NO - 51 -
------	----------	--------------	-----	----	-----------

	Let	и Цу	s Il	e Ala	a Ala	ı Phe	Asn	ı Ile	∈ Glr	n Thr	Phe	e Glv	Gli	ı Th	r Lys
	-	•			3	•				10	)				15
5					20					25	,				Ser 30
	Arg	ј Ту	r Asp	ρIle	Ala 35	Leu	Val	Glr	ı Glu	Val	Arg	Asp	Ser	His	45
	Thr	Al	a Val	l Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55		Gln	Asp	Ala	Pro 60
10	Asp	Th.	r Tyr	r His	Cys 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Ly	s Glu	ı Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
15	Ala	Va:	l Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	o Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	? Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
20	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
25	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
<b>3</b> 0	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala .	Ala	Tyr	Gly 2 <b>4</b> 0
35	Leu	Ser	Asp	Gln	Leu . 245	Ala (	Gln .	Ala	Ile	Ser . 250	Asp :	His '	Tyr	Pro	Val 255
	Glu	Val	Met		Lys 260										
	(2) T	NEOI	OMATE	ONE	כם כי	DO	<b></b>								

(2) INFORMATION FCR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 260 amino acids
- (B) TYPE: Amino Acid
- (D) TOPOLOGY: Linear

5	(xi	) SE	QUEN	CE DI	ESCR	IPTI	ON:	SEQ	ID N	0:52	:				
	Leu 1	Lys	Ile	Ala i	Ala i	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala '	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
10	Arg	Tyr	Asp	Ile .	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
15	Asp	Thr	Tyr	His	Lys 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Туг 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
20	Asn	Asp	Thr	Phe	<b>As</b> n 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	11e 130	Val	Pro	Leu	His	Ala 135
25	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145		Leu	Туг	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160		Asp	Val	Met	<b>Leu</b> 165
	Met	: Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175		Arg	Pro	Ser	Gln 180
30	Trp	Ser	: Ser	· Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190		Phe	Gln	Trp	195
	Il€	e Pro	Asp	Ser	Ala 200		Thr	Thr	Ala	Thr 209		Thr	His	s Cys	210
35	Ту	r Asp	Arg	, Ile	Val 215		Ala	Gly	/ Met	220		ı Arg	g Glλ	r Ala	225
	Va.	l Pro	o Ası	Ser	230		ı Pro	) Phe	e Asr	23!		n Ala	a Ala	а Туі	240
	Le	u Se	r Asj	o Glr	. Leu 245		a Glr	n Ala	a Ile	25		p Hi	s Ту:	r Pro	o Val 255

Glu Val Met Leu Lys 260

5

### (2) INFORMATION FOR SEQ ID NO:53:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 260 amino acids

(B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:53:

			_					_							
10	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
15	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	<b>Le</b> u <b>5</b> 5	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Met 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
20	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
25	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	туr	Asp	Val 150
30	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	<b>Asn</b> 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
35	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225

-79-

Val Pro Asp Ser Ala Leu Pro Phe Asn Phe Gln Ala Ala Tyr Gly 235 Leu Ser Asp Gln Leu Ala Gln Ala Ile Ser Asp His Tyr Pro Val 250 Glu Val Met Leu Lys 260 (2) INFORMATION FOR SEQ ID NO:54: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 260 amino acids (B) TYPE: Amino Acid 10 (D) TOPOLOGY: Linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:54: Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys Met Ser Asn Ala Thr Leu Val Ser Tyr Ile Val Gln Ile Leu Ser 15 Arg Tyr Asp Ile Ala Leu Val Gln Glu Val Arg Asp Ser His Leu Thr Ala Val Gly Lys Leu Leu Asp Asn Leu Asn Gln Asp Ala Pro 2.0 Asp Thr Tyr His Ser Val Val Ser Glu Pro Leu Gly Arg Asn Ser Tyr Lys Glu Arg Tyr Leu Phe Val Tyr Arg Pro Asp Gln Val Ser 25 Ala Val Asp Ser Tyr Tyr Tyr Asp Asp Gly Cys Glu Pro Cys Gly Asn Asp Thr Phe Asn Arg Glu Pro Ala Ile Val Arg Phe Phe Ser Arg Phe Thr Glu Val Arg Glu Phe Ala Ile Val Pro Leu His Ala 30 Ala Pro Gly Asp Ala Val Ala Glu Ile Asp Ala Leu Tyr Asp Val Tyr Leu Asp Val Gln Glu Lys Trp Gly Leu Glu Asp Val Met Leu 35 Met Gly Asp Phe Asn Ala Gly Cys Ser Tyr Val Arg Pro Ser Gln 170 175 Trp Ser Ser Ile Arg Leu Trp Thr Ser Pro Thr Phe Gln Trp Leu 190

	Ile	e Pro	⊃ Asp	Ser	200	Asp	Thr	Thr	Ala	a Thr 205		Thi	r His	s Cys	5 Ala 210
	Tyr	Asp	Arg	; Ile	215		Ala	Gl}	′ Met	220		Arg	g Gly	⁄ Ala	225
5	Val	Pro	as,	Ser	Ala 230	Leu	Pro	Phe	: Asr	n Phe 235		Ala	a Alā	Туг	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	ser 250		His	туг	Pro	Val 255
10	Glu	Val	. Met	. Leu	Lys 260										
	(2)	INFC	RMAT	NOI	FOR	SEQ	ID N	O: <b>5</b> 5	:						
15	(	(	A) L B) T	ENGT YPE :	CHAR H: 2 Ami OGY:	60 a no A	mino cid		ds						
	(x	i) S	EQUE	NCE	DESC	RIPT	ION:	SEQ	ID	<b>N</b> O : 5	5 :				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
20	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
25	Asp	Thr	Tyr	His	Tyr 65	Val	Cys	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Туг 80	Leu	Phe	Val	туr	Arg 85	Pro	Asp	Gln	Val	Ser 90
30	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
35	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	<b>Le</b> u 165

	Met Gly	Asp I		Asn i	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp Ser	Ser 3		Arg 1	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
5	Ile Pro	Asp S		Ala . 200	Asp	Thr	Thr	Ala	Thr 205	Prc	Thr	Hıs	Cys	Ala 210
	Tyr Asp	Arg		Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	<b>Val</b> 225
10	Val Pro	Asp		Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu Ser	Asp		Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Туг	Pro	Val 255
	Glu Val	Met		Lys 260										
15	(2) INFO	RMATI	ON F	OR S	EQ 1	ID N	0:56	:						
	(	EQUEN A) LE B) TY D) TO	NGTH	: 26 Amir	0 an	mino cid		is						
20	(xi) S	EQUEN	ICE I	ESC	RIPT	ON:	SEQ	ID	<b>N</b> O : 5	5:				
	Leu Lys 1	lle	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
	Met Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
25	Arg Ty	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40		qaA	Ser	His	Leu 45
	Thr Ala	a Val	Gly	Lys 50	Leu	Let	a Asp	Asn	Leu 55		Glr	a Asp	Ala	Pro 60
30	Asp Th	r Tyr	His	Tyr 65		Asp	Ser	Glu	70		Gly	⁄ Ar⊆	g Asn	Ser 75
	Tyr Ly	s Glu	Arg	Tyr 80		Phe	e Val	Тут	Arg 85		Asp	o Glr	ı Val	. Ser 90
	Ala Va	l Asp	Ser	Tyr 95		ту	r Asp	Asp	Gly 100		s Glu	u Pro	o Cys	105
3 5	Asn As	p Thr	Phe	Asn 110		g Gl	u Pro	Ala	a Ile		l Ar	g Phe	e Phe	ser 120
	Arg Ph	e Thr	Glu	Val		g Gl	u Phe	e Ala	a Ile 130		l Pr	o Lei	u His	s Ala 135

					110	,				14	5				p <b>Val</b> 150
	ту	r Le	eu As	sp Va	l Gln 155	ı Glu	ı Lys	Tr	p Gl	y Let 160	u Glu	Asp	Val	Ме	t <b>Le</b> u 165
5	Ме	t Gl	ly As	p Ph	e Asn 170	Ala	Gly	Cys	s Se	r Tyr 175	r Val	Arg	Pro	Ser	Gln 180
	Tr	p Se	er Se	r Ile	e Arg 185	Leu	Trp	Thr	Se:	r Pro	Thr	Phe	Gln	Trp	Leu 195
10	Il	e Pr	o As	p Sei	r Ala 200	Asp	Thr	Thr	- Alá	a Thr 205	Pro	Thr	His	Суя	Ala 210
	Ту	r As	p Ar	g Ile	215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Va:	l Pr	o As <sub>l</sub>	p Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
15	Let	ı Se	r Ası	o Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	ı Va	l Met	Leu	Lys 260										
	(2)	INFO	ORMAT	CION	FOR S	EQ I	D NC	:57	:						
20	(	•	(A) L (B) I	ENGT:	CHARA H: 26 Amin OGY:	0 am	ino id	CS: acid	is						
	(x	i) s	EQUE	NCE 1	DESCR	IPTI	ON:	SEQ	ID 1	NO : 57	:				
25	Leu 1	Lys	Ile	Ala	Ala 5	Phe .	Asn	Ile	Gln	Thr 10	Phe	Gly (	Glu '	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr :	Leu '	Val	Ser	Tyr	Ile 25	Val (	Gln :	Ile 1	Leu	Ser 30
30	Arg	Tyr	Asp	Ile	Ala 1	Leu 1	Val (	Gln	Glu	Val	Arg Z	Asp S	Ser I	lis	Leu 45
	Thr	Ala	Val	Gly	Lys I 50	Leu I	Leu i	Asp .	Asn	Leu . 55	Asn (	Gln A	Asp A	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr \ 65	/al F	His S	Ser	Glu	Pro 1	Leu (	Sly A	arg A	sn	Ser 75
35	Tyr	Lys	Glu	Arg	Tyr I	Leu F	Phe V	/al /	Tyr	Arg I 85	Pro A	sp G	In V	al:	Ser 90
	Ala	Val	Asp	Ser	Tyr 1 95	yr T	yr A	sp A		Gly (	lys G	lu P	ro C		31y 105

	Asn	Asp	Thr	Phe	<b>Asn</b>	Arg	Glu	Pro	Ala	11e 115	Val	Arg	Pne	Phe	120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
5	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
10	Met	Glγ	/ Asp	Phe	<b>As</b> n 170		Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Sei	r Ser	Ile	Arg 185		Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	o Asp	Ser	Ala 200		) Thr	Thr	Ala	Thr 205		Thr	His	Cys	Ala 210
15	Туг	As	p Arg	g Ile	215		Ala	Gly	Met	<b>Leu</b> 220	Leu	Arg	g Gly	/ Ala	Val 225
	Va]	Pr	o Asj	p Sei	230		ı Pro	) Phe	. Asr	235		n Ala	a Alá	а Туг	Gly 240
20	Lev	ı Se	r As	p Gli	n Lei 24!		a Glr	n Ala	a Ile	250	As <sub>I</sub>	) Hi:	s Ту:	r Pro	255
	Gl <sup>.</sup>	u Va	ıl Me	t Le	u Ly. 26										
	(2)	INE	FORMA	TION.	FOR	SEQ	ID :	NO : 5	B :						
25		(i)	(A) (B)	LENG TYPE	TH:	260 ino	ERIS amin Acid near	o ac							
	(	xi)	SEQU	JENCE	DES	CRIF	MOIT	: SE	Q ID	<b>N</b> O:	58:				
30	Le	u L	ys I	le Al	a Al	a Ph	ne As	in Il	e Gl	n Th	r Ph	e Gl	y Gl	u Th	r Lys
	Me	et S	er A	sn Al		ır Le 20	eu Va	al Se	r Ty	r Il 2	e Va	al Gl	in Il	ie Le	u Ser 30
	<b>A</b> :	rg T	yr A	sp I		la Lo	eu Vá	al Gl	ın Gl		11 A1	cg As	sp Se	er Hi	.s <b>Le</b> u <b>4</b> 5
35	T	hr A	la V	al G		ys L 50	eu Le	eu As	sp As	sn Le	eu A: 55	sn G	ln A	sp Al	la Pro 60
	A	sp 1	Thr T	yr H		yr V 65	al M	et S	er G		rc L	eu G	ly A	rg A	sn Ser 75

	Tyr Lys Glu	Arg Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Sei 90
	Ala Val Asp	Ser Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gl <sub>y</sub> 109
5	Asn Asp Thr 1	Phe Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg Phe Thr (	Glu Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
10	Ala Pro Gly A	Asp Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Туг	Asp	Val
	Tyr Leu Asp \	/al Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met Gly Asp I	Phe Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Glr 180
15	Trp Ser Ser	le Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile Pro Asp S	Ser Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
20	Tyr Asp Arg 1	le Val 215	Val .	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val Pro Asp S	Ser Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu Ser Asp G	ln Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
25	Glu Val Met I	Leu Lys 260										
	(2) INFORMATIO	N FOR S	SEQ II	D NO	:59:							
30	(B) TYP	E CHARA IGTH: 26 E: Amir OLOGY:	0 am:	ino 1d		.s						
	(x1) SEQUENC	E DESCR	RIPTIO	: AC	SEQ	ID N	10 : 5 9	:				
	Leu Lys Ile A	la Ala 5	Phe 1	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
35	Met Ser Asn A	la Thr 20	Leu V	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg Tyr Asp I	le Ala 35	Leu 1	Val (	Gln	Glu	Val	Arg	Asp	Ser	His	Leu 45

	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	<b>Le</b> u 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Pro	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
5	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
10	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	<b>As</b> p	Ala	Leu	Tyr	Asp	Val 150
15	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
20	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
25	Val	Pro	Asp	Ser	Ala 230		Pro	Phe	Asn	Phe 235		Ala	Ala	Tyr	Gly 240
	Leu	. Ser	. Yab	Gln	Leu 245		Gln	Ala	Ile	Ser 250		His	Tyr	Pro	<b>Val</b> 255
30	Glu	Val	. Met	Leu	Lys 260										
	(2)	INFO	RMAT	CION	FOR	SEQ	ID N	0:60	):						
	(		-				ERIST								
			(A) I (B) T				mino Acid	aci	ds						
35			(D) 7												

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:60:

Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys
1 5 10 15

	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
5	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Arg	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
10	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
15	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	<b>Val</b> 150
20	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Ąsp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
25	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	<b>Le</b> u 220	Leu	Arg	Gly	Ala	Val 225
30	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										

### 35 (2) INFORMATION FOR SEQ ID NO:61:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 260 amino acids
  - (B) TYPE: Amino Acid
  - (D) TOPOLOGY: Linear

/ \	anarmuan	DESCRIPTION			
(X1)	SEQUENCE	DESCRIPTION:	SEO	ID	NO · 61 ·

	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr	Phe	Gly	Glu	Thr	Lys 15
5	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
10	Asp	Thr	Tyr	His	Tyr 65	Val	Ser	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
15	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	qaA	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
20	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile		Ala	Leu	Tyr	Asp	
					2.0					145					150
	Tyr	Leu	Asp	Val		Glu	Lys	Trp	Gly		Glu	Asp	Val	Met	
25		Leu Gly			Gln 155					Leu 160					Leu 165
25	Met		Asp	Phe	Gln 155 Asn 170	Ala	Gly	Cys	Ser	Leu 160 Tyr 175	Val	Arg	Pro	Ser	Leu 165 Gln 180
25	Met Trp	Gly	Asp Ser	Phe Ile	Gln 155 Asn 170 Arg 185	Ala Leu	Gly	Cys Thr	Ser Ser	Leu 160 Tyr 175 Pro 190	Val Thr	Arg Phe	Pro Gln	Ser Trp	Leu 165 Gln 180 Leu 195
<b>25</b>	Met Trp Ile	Gly	Asp Ser Asp	Phe Ile Ser	Gln 155 Asn 170 Arg 185 Ala 200	Ala Leu Asp	Gly Trp Thr	Cys Thr	Ser Ser Ala	Leu 160 Tyr 175 Pro 190 Thr 205	Val Thr Pro	Arg Phe Thr	Pro Gln His	Ser Trp Cys	Leu 165 Gln 180 Leu 195 Ala 210
	Met Trp Ile	Gly Ser Pro	Asp Ser Asp	Phe Ile Ser	Gln 155 Asn 170 Arg 185 Ala 200 Val 215	Ala Leu Asp	Gly Trp Thr	Cys Thr Thr	Ser Ser Ala	Leu 160 Tyr 175 Pro 190 Thr 205 Leu 220	Val Thr Pro	Arg Phe Thr	Pro Gln His	Ser Trp Cys	Leu 165 Gln 180 Leu 195 Ala 210 Val 225
	Met Trp Ile Tyr Val	Gly Ser Pro	Asp Ser Asp Arg	Phe Ile Ser Ile	Gln 155 Asn 170 Arg 185 Ala 200 Val 215 Ala 230	Ala Leu Asp Val	Gly Trp Thr Ala	Cys Thr Thr Gly Phe	Ser Ser Ala Met	Leu 160 Tyr 175 Pro 190 Thr 205 Leu 220 Phe 235	Val Thr Pro Leu Gln	Arg Phe Thr Arg	Pro Gln His Gly	Ser Trp Cys Ala	Leu 165 Gln 180 Leu 195 Ala 210 Val 225 Gly 240

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 260 amino acids
- (B) TYPE: Amino Acid
- (D) TOPOLOGY: Linear

15

35

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys
1 5 10 15

Met Ser Asn Ala Thr Leu Val Ser Tyr Ile Val Gln Ile Leu Ser

10 Arg Tyr Asp Ile Ala Leu Val Gln Glu Val Arg Asp Ser His Leu 35 40 45

Thr Ala Val Gly Lys Leu Leu Asp Asn Leu Asn Gln Asp Ala Pro

Asp Thr Tyr His Tyr Val Val Lys Glu Pro Leu Gly Arg Asn Ser
65 70 75

Tyr Lys Glu Arg Tyr Leu Phe Val Tyr Arg Pro Asp Gln Val Ser 80 85 90

Ala Val Asp Ser Tyr Tyr Tyr Asp Asp Gly Cys Glu Pro Cys Gly
95 100 105

20 Asn Asp Thr Phe Asn Arg Glu Pro Ala Ile Val Arg Phe Phe Ser 110 115 120

Arg Phe Thr Glu Val Arg Glu Phe Ala Ile Val Pro Leu His Ala 125 130 135

Ala Pro Gly Asp Ala Val Ala Glu Ile Asp Ala Leu Tyr Asp Val
140 145 150

Tyr Leu Asp Val Gln Glu Lys Trp Gly Leu Glu Asp Val Met Leu 155 160 165

Met Gly Asp Phe Asn Ala Gly Cys Ser Tyr Val Arg Pro Ser Gln 170 175 180

30 Trp Ser Ser Ile Arg Leu Trp Thr Ser Pro Thr Phe Gln Trp Leu 185 190 195

Ile Pro Asp Ser Ala Asp Thr Thr Ala Thr Pro Thr His Cys Ala 200 205 210

Tyr Asp Arg Ile Val Val Ala Gly Met Leu Leu Arg Gly Ala Val

Val Pro Asp Ser Ala Leu Pro Phe Asn Phe Gln Ala Ala Tyr Gly
230 235 240

Leu Ser Asp Gln Leu Ala Gln Ala Ile Ser Asp His Tyr Pro Val 245 250 255

Glu Val Met Leu Lys 260

5

## (2) INFORMATION FOR SEQ ID NO:63

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 260 amino acids
- (B) TYPE: Amino Acid
- (D) TOPOLOGY: Linear

# (x1) SEQUENCE DESCRIPTION: SEQ ID NO:63:

	(X1	.) SE	,QUEN	CE DI	ESCR.	IPII	OIV:	SEQ	10 14	0.03	•				
10	Leu 1	Lys	Ile	Ala i	Ala :	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
15	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Met	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
20	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
25	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
				Asp	140					145					150
30				Val	155					160					165
				) Phe	170					175					180
	Trj	p Set	r Sei	r Ile	Arg 185		Trp	Thi	r Ser	Pro 190		Phe	Glr	1 Trp	195
35	Il	e Pr	o Ası	p Ser	Ala 200		Thi	Th:	r Ala	Thr 205		Thr	Hi	s Cys	210
	Ту	r As	p Ar	g Ile	215		l Ala	a Gl	y Met	220		ı Arç	g Gl	y Ala	a Val 225

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 WO 96/26279

 Val
 Pro
 Asp
 Ser
 Ala Leu Pro Phe 230
 Phe 235
 Ser
 Ala Ala Tyr Gly 240

 Leu Ser
 Asp
 Gln Ala Gln Ala Ile Ser Asp His Tyr Pro Val 255

5 Glu Val Met Leu Lys 260

- (2) INFORMATION FOR SEQ ID NO:64:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 260 amino acids
- 10 (B) TYPE: Amino Acid
  - (D) TOPOLOGY: Linear
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

Leu Lys	Ile Ala	Ala	Phe	Asn	Ile	Gln	Thr	Phe	Glv	Glu	Thr	Tarc
3		_							O- 7	Giu	1 111	цуs
-		2					10					15

- Met Ser Asn Ala Thr Leu Val Ser Tyr Ile Val Gln Ile Leu Ser 20 25 30
  - Arg Tyr Asp Ile Ala Leu Val Gln Glu Val Arg Asp Ser His Leu
    35 40 45
- Thr Ala Val Gly Lys Leu Leu Asp Asn Leu Asn Gln Asp Ala Pro
  50 55 60
  - Asp Thr Tyr His Tyr Val Val Arg Glu Pro Leu Gly Arg Asn Ser
    65 70 75
  - Tyr Lys Glu Arg Tyr Leu Phe Val Tyr Arg Pro Asp Gln Val Ser
- 25 Ala Val Asp Ser Tyr Tyr Tyr Asp Asp Gly Cys Glu Pro Cys Gly
  95 100 105
  - Asn Asp Thr Phe Asn Arg Glu Pro Ala Ile Val Arg Phe Phe Ser
- Arg Phe Thr Glu Val Arg Glu Phe Ala Ile Val Pro Leu His Ala 30 125 130 135
  - Ala Pro Gly Asp Ala Val Ala Glu Ile Asp Ala Leu Tyr Asp Val 140 145 150
  - Tyr Leu Asp Val Gln Glu Lys Trp Gly Leu Glu Asp Val Met Leu 155 160 165
- Met Gly Asp Phe Asn Ala Gly Cys Ser Tyr Val Arg Pro Ser Gln
  170 175 180
  - Trp Ser Ser Ile Arg Leu Trp Thr Ser Pro Thr Phe Gln Trp Leu 185 190 195

-91-

	Ile Pr	co A	sp S		la 1	Asp	Thr	тŀ	ır A	la	Thr 205	Pr	0 T	hr	His	C	ys .	Ala 21	<b>a</b> O
	Tyr As	вр А	Arg I		/al ' 215	Val	Ala	G)	ly M	let	Leu 220	Le	u A	.rg	Gly	/ A	la	Va 22	1 5
5	Val P	ro A	Asp S		Ala 230	Leu	Pro	Pl	he A	Asn	Phe 235	Gl	n A	la	Ala	аТ	yr	G1 24	У О
	Leu S	er i	Asp (		Leu 2 <b>4</b> 5	Ala	Gln	<b>A</b>	la :	Ile	Ser 250	As	sp F	lis	ТУ	r F	ro	Va 25	1 5
10	Glu V	al 1	Met 1		Lys 260														
	(2) IN	FOR	MATI	ON F	OR S	EQ	ID 1	10:	65:										
15	(i)	(A (E (D	QUEN LE TY TO	NGTH PE: POLC	: 26 Amir )GY:	o a o A Lin	mino cid ear	o <b>a</b>	icid		NO.								
			EQUEN											~ 1	<b>a</b> 1		mb		
	Leu I	Lys	Ile	Ala	Ala 5	Phe	e As	n I	Ile	Glr	1 Th	r P .0	ne	GIZ	/ G.	Lu	1111	ים	ys 15
20	Met :	Ser	Asn	Ala	Thr 20		ı Va	1 :	Ser	Туз	r Il 2	.e V !5	al	Gli	n I	le	Leu	S	er 30
	Arg	Tyr	Asp	Ile	Ala		u Va	al (	Gln	Gl	u Va	al F	Arg	As	p S	er	His	L	eu 45
	Thr	Ala	Val	Gly	Lys 50		u Le	eu	Asp	As	n Le	eu <i>1</i> 55	Asn	G1	n A	sp	Alá	a F	60 60
25	Asp	Thr	Tyr	His	Ту: 65		1 Va	al	Ser	Al	a P	ro 1 70	Leu	Gl	y A	rg	Ası	n S	<b>5e</b> r 75
	Tyr	Lys	: Glu	Arg	у Ту: 8		eu P	he	Val	ту	r A	rg 85	Pro	As	e g	ln	Va	1 5	90
30	Ala	Va]	L Asp	Sei	ту 9		r T	yr	Asp	As	sp G 1	1y 00	Cys	G)	lu I	ro	Су	s (	Gly 105
	Asn	Ası	p Thi	r Phe	e As		rg G	ilu	Pro	A]	la I	le 15	Val	A	rg I	?he	Ph	e	<b>Se</b> r 120
	Arg	Ph	e Thi	r Gl	u Va 12		rg G	slu	Phe	e A.	la I	le 130	Val	. P:	ro!	Leu	. Hi	s	Ala 135
35	Ala	Pr	o Gl	y As	p Al 14		al A	Ala	Gl	u I	le A	<b>Asp</b>	Ala	a L	eu	Туг	: As	p	<b>Va</b> l 150
	Tyr	Le	u As	p Va		in G	lu I	Lys	Tr	рG	ly 1	Leu 160	Gl	u A	.sp	Va:	l Me	e t	Leu 165

	Met	Gly	Asp	Phe	<b>As</b> n 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
5	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	<b>A</b> la 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
10	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										
15	(2)	INFO	TAMS	ON I	FOR S	SEQ I	ID N	D: <b>6</b> 6:	;						
	(	()	EQUEN A) LI B) TY	ENGTH PE:	H: 26 Amir	0 an	mino cid		is						
20	(x.	i) SI	EQUE	NCE I	DESC	RIPT	ON:	SEQ	ID 1	10 : 66	5:				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile	Val	Gln	Ile	Leu	
25										25					Ser 30
	Arg	Tyr	Asp	Ile		Leu	Val	Gln	Glu				Ser		30
		Tyr Ala			Ala 35					Val 40	Arg	Asp		His	30 Leu 45
30	Thr		Val	Gly	Ala 35 Lys 50	Leu	Leu	Asp	Asn	Val 40 Leu 55	Arg Asn	<b>A</b> sp	Asp	His Ala	30 Leu 45 Pro 60
30	Thr Asp	Ala	Val Tyr	Gly His	Ala 35 Lys 50 Tyr 65	<b>Leu</b> Val	<b>Le</b> u Val	<b>As</b> p	<b>As</b> n Cys	Val 40 Leu 55 Pro 70	Arg Asn Leu	Asp Gln Gly	<b>A</b> sp	His Ala Asn	30 Leu 45 Pro 60 Ser 75
30	Thr Asp Tyr	Ala	Val Tyr Glu	Gly His	Ala 35 Lys 50 Tyr 65 Tyr 80	<b>Leu</b> Val Leu	<b>Le</b> u Val Phe	Asp Ser Val	<b>As</b> n Cys Tyr	Val 40 Leu 55 Pro 70 Arg 85	Arg Asn Leu Pro	Asp Gln Gly Asp	Asp Arg	His Ala Asr. Val	30 Leu 45 Pro 60 Ser 75 Ser 90
30	Thr Asp Tyr Ala	Ala Thr Lys	Val Tyr Glu Asp	Gly His Arg Ser	Ala 35 Lys 50 Tyr 65 Tyr 80 Tyr 95	Leu Val Leu Tyr	Leu Val Phe Tyr	Asp Ser Val	Asn Cys Tyr Asp	Val 40 Leu 55 Pro 70 Arg 85 Gly 100	Arg Asn Leu Pro	Asp Gln Gly Asp	Asp Arg Gln Pro	His Ala Asn Val	30 Leu 45 Pro 60 Ser 75 Ser 90 Gly 105

	Ala	Prc	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	<b>As</b> p 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	<b>Le</b> u 160	Glu	Asp	Val	Met	Leu 165
5	Met	Gly	Asp	Phe	<b>Asn</b> 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
10	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
15	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	<b>Lys</b> 260										
	(2)	INFOI	TAMS	ION I	FOR S	SEQ :	ID <b>N</b> (	0:67	:						
20	( :	(1	A) LI 3) TY	ENGTI YPE :	CHARU H: 26 Amir DGY:	50 at	mino cid		is						
20		(1	A) LE 3) TY 0) TO	ENGTI YPE: OPOLO	H: 26 Amir DGY:	50 at no Ac Line	mino cid ear	acio		۷O : 6 <sup>-</sup>	7:				
20	(x:	() (I	A) LI B) TY D) TO	ENGTI YPE: OPOLO	H: 26 Amir DGY:	50 ar no Ac Line	mino cid ear	acid	ID 1			Gly	Glu	Thr	Lys 15
	(x: Leu 1	() (I (I i) SI	A) LE B) TY D) TO EQUED	ENGTI YPE: OPOLO NCE I	H: 26 Amir DGY: DESCR	50 ar no Ad Line RIPT:	mino cid ear ION:	acid SEQ	ID i	Thr 10	Phe				15
	(x: Leu 1 Met	() (I (I i) SI Lys	A) LH B) TY C) TO EQUER Ile Asn	ENGTH YPE: DPOLO NCE I Ala	H: 26 Amir DGY: DESCRI Ala 5 Thr 20	50 ar no Ao Line RIPT: Phe	mino cid ear ION: Asn Val	seQ Ile	ID f	Thr 10 Ile 25	Phe Val	Gln	Ile	Leu	15 Ser 30
25	(x: Leu 1 Met	(I (I (I Lys Ser	A) LH B) TY C) TO EQUER HER ASD	ENGTH YPE: DPOLO NCE I Ala Ala Ile	H: 26 Amir DGY: DESCR Ala 5 Thr 20 Ala 35	FOR THE LEU  Leu  Leu  Leu	mino cid ear ION: Asn Val	SEQ Ile Ser	ID i Gln Tyr Glu	Thr 10 Ile 25 Val 40	Phe Val Arg	Gln Asp	Ile Ser	Leu His	15 Ser 30 Leu 45
25	(x: Leu 1 Met Arg	(I (I (I ) (I ) SE Ser	A) LH B) TY D) TO EQUER  Ile  Asn  Asp	ENGTH YPE: DPOLO NCE I Ala Ala Ile	H: 26 Amir DGY: DESCR Ala 5 Thr 20 Ala 35 Lys 50	Fig. 20 September 1	mino cid ear ION: Asn Val Val	SEQ Ile Ser Gln	ID t Gln Tyr Glu Asn	Thr 10 Ile 25 Val 40 Leu 55	Phe Val Arg	Gln Asp Gln	Ile Ser Asp	Leu His	15 Ser 30 Leu 45 Pro 60
25	Leu 1 Met Arg Thr	(I (I (I ) Lys Ser Tyr	A) LEB) TY D) TO EQUER Ile Asn Asp Val	ENGTH YPE: DPOLO NCE I Ala Ala Ile Gly	H: 26 Amir DGY: DESCRI Ala 5 Thr 20 Ala 35 Lys 50 Tyr 65	Fig. 20 Section 10 Acres 10 Ac	mino cid ear ION: Asn Val Val Leu Val	sEQ Ile Ser Gln Asp	ID N Gln Tyr Glu Asn Met	Thr 10 Ile 25 Val 40 Leu 55 Pro 70	Phe Val Arg Asn Leu	Gln Asp Gln	Ile Ser Asp	Leu His Ala Asn	15 Ser 30 Leu 45 Pro 60 Ser 75

	As	n As	p Th	r Phe	≥ <b>As</b> r	Arg	r Gli	Pro	Ala	Ile 115		Arg	, Ph€	e Ph	e Se
	Arg	g Ph	e Th	r Glı	1 Val 125	Arg	Glu	Phe	Ala	Ile 130		Pro	Let	Hi.	s Ala
5	Ala	a Pr	o Gl	y Asp	140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Туг	Ası	2 Val
	Туг	Le	u Asj	p Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Let 165
10	Met	: Gl	y Ası	p Phe	170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Sei	Glr 180
	Trp	Se	r Sei	r Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
15	Tyr	Asp	Arg	, Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 2 <b>4</b> 0
20	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										
	(2)	INFO	RMAT	ION I	FOR S	SEQ I	D NO	9:68:							
25	(.	(	A) L B) T	NCE ( ENGTI YPE : OPOL(	d: 26 Amin	0 am 10 Ac	ino id		ls						
	(x:	i) s	EQUE	NCE I	DESCR	IPTI	ON:	SEQ	ID N	0:68	:				
30	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile ' 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala . 35	Leu '	Val	Gln	Glu '	Val 2	Arg .	Asp	Ser	His	Leu 45
35	Thr	Ala	Val	Gly	Lys :	Leu :	Leu .	Asp .	Asn 1	Leu 1 55	Asn (	Gln .	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr ' 65	Val 1	√al :	Ser (	Glu I	Pro I 70	Seu (	Gly A	Arg	Asn	Ser 75

	Tyr	Lys	Glu	Arg	<b>Tyr</b> 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Туг	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
5	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Сув	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
10	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	<b>As</b> p 1 <b>4</b> 5	Ala	Leu	Tyr	Asp	Val 150
	Туг	Leu	Asp	Val	Gln 155		Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170		Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
15	Trp	Ser	Ser	Ile	Arg		Trp	Thr	Ser	Pro 190		Phe	Gln	Trp	Leu 195
	Ile	Pro	o Asp	Ser	Ala 200		Thr	Thr	Ala	205		Thr	His	Cys	210
20	туз	r Asj	p Arg	g Ile	e Val		l Ala	a Gly	/ Met	220		Arg	g Gly	/ Ala	225
	Va:	l Pr	o Ası	p Se	r Ala 23		u Pro	o Phe	e Ası	n Phe 239		Ala	a Ala	а Туз	240
	Le	u Se	r Asj	p Gl:	n Le		a Gl	n Al	a Il	e Sei 25	r Asp	Hi:	з Ту:	r Pro	255
25	Gl	u Va	l Me	t Le	u Ly 26										
	(2)	INF	ORMA	TION	FOR	SEQ	ID	<b>N</b> O : 6	9:						
30		(i)	(B)	LENG TYPE	TH:	260 nino	ERIS amin Acid near	o ac							
		(xi)	SEQU	JENCE	DES	SCRIF	10IT	: SE	EQ II	NC:	69:				
	Le	eu Ly 1	ys Il	le Al	la Al	la Pl	ne As	sn Il	le Gl		r Ph	ie Gl	y Gl	u Th	ir Lys 15
35	Me	et S	er As	sn Al		nr Le 20	eu Va	al Se	er Ty		Le Va 25	il Gl	ln I	ie Le	eu Ser 30
	A	rg T	yr A	sp I		la L	eu V	al G	ln G	lu Vá	al Ar 40	g As	sp Se	er H	is Lev

	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	туr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
5	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
10	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Glu	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	<b>Va</b> l
15	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	<b>Le</b> u 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
20	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	qeA	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
25	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
30	Glu	Val	Met	Leu	Lys 260										
	(2) 1	NFOE	TAMS	ON F	FOR S	EQ I	D NO	): <b>7</b> 0:							
	(i	(2	A) LE	NCE C ENGTH PE:	1: 26	0 am	nino		ls						
35				POLC											

- - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys 1 10

	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	туr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	Hıs	Leu 45
5	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
10	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Туг 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Gly	Ile 115	Val	Arg	Phe	Phe	Ser 120
15	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
20	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185		Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
25	Ile	Pro	Asp	Ser	Ala 200		Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Туг	Asp	Arg	Ile	Val 215		Ala	Gly	Met	Leu 220		Arg	Gly	Ala	. Val
30	Va]	l Pro	Asp	Ser	Ala 230		ı Pro	Phe	: Asn	Phe 235		Ala	Ala	Туг	Gly 240
	Let	ı Sei	Ası	o Glr	1 Leu 245		a Glr	n Ala	lle	Ser 250		His	туг	Pro	Val 255
	Gli	ı Val	l Met	. Leu	1 Lys 260										

- 35 (2) INFORMATION FOR SEQ ID NO:71:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 260 amino acids
    - (B) TYPE: Amino Acid
    - (D) TOPOLOGY: Linear

(xi)	SEQUENCE	DESCRIPTION:	SEO	ΤD	NO - 71 -
		DECEMBER 1 LOIV.	<u> </u>	T L	IN(): / 1:

	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr	Phe	Gly	Glu	Thr	Lys 15
5	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	Hıs	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
10	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
15	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	His	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
20	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
25	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	qaA	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
30	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 2 <b>4</b> 0
35	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										

(2) INFORMATION FOR SEQ ID NO:72:

	(i	(A (B	L) LE	ICE C NGTH PE: POLO	: 26 Amın	0 am	ino id		s						
5	( <b>x</b> )	) SE	QUEN	ICE D	ESCR	IPTI	ON:	SEQ	ID N	0:72	:				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr :	Lys 15
	Met	ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu .	ser 30
10	Arg	туr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
15	Asp	Thr	Tyr	His	Туг 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
20	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Lys	Ile 115	Val	Arg	Phe	Phe	S <b>er</b> 120
	Arg	Phe	Thr	Glu	Val 125		Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
25	Ala	Pro	o Gly	Asp	Ala 140		Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val
	Туг	Lev	Asp	val	Gln 155		ı Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Let 165
	Met	Gly	/ Asp		170					Tyr 175				Ser	Glr 180
30	Tr	Se:	r Sei	r Ile	arg 185		ı Trp	o Thr	Ser	Pro 190		Phe	Gln	Trp	Le:
	110	e Pro	o Ası	p Ser	Ala 200		p Thi	r Thr	Ala	Thr 205		Thr	His	Cys	Ala 21
35	Ty	r As	p Ar	g Ile	e Val		l Ala	a Gly	/ Met	220		Arg	g Gly	Ala	Va 22
	Va	l Pr	o As	p Sei	r Ala 23		u Pr	c Phe	e As:	n Phe 235		Ala	a Ala	Tyr	G1 24
	Le	u Se	r As	p Gli	n Le		a Gl	n Ala	a Il	e Ser 250		> His	з Туг	Pro	Va 25

Glu Val Met Leu Lys 260

# (2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 260 amino acids

- (B) TYPE: Amino Acid
- (D) TOPOLOGY: Linear

## (xi) SEQUENCE DESCRIPTION: SEO ID NO:73:

	(X1) S	SEQUENCE	DESCRIE	: NOIT	SEQ	ID	<b>N</b> O:73	3 :			
10	Leu Lys 1	Ile Al	a Ala Ph 5	e Asn	lle	Gln	Thr 10	Phe (	Sly Gl	u Th:	r Lys 15
			a Thr Le 20				25				30
			e Ala Le 35				40				<b>4</b> 5
15			y Lys Le 50				55				<b>6</b> 0
			Tyr Va 65				70				75
20			Tyr Lei 80				85				90
			Tyr Tyi 95				100				105
2.5	Asn Asp		110				115				120
25	Arg Phe		125				130				135
	Ala Pro		140				145				150
30	Tyr Leu		135				160				165
	Met Gly		170				175				180
35	Trp Ser		103			-	190				195
33	Ile Pro		200			2	205				210
	Tyr Asp	arg lle	Val Val 215	Ala (	Gly M	1et I	Leu Le 220	eu Ar	g Gly		Val 225

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WO 96/26279

	Val Pro A		la Leu 30	ı Pro	Phe A	sn Pl	ne Gl 35	n Ala	a Al	а Ту	r Gl	7 O 7 A.
	Leu Ser A		eu Ala 45	a Gln	Ala 1	lle Se	er As 50	p Hi	s Ty	r Pr	0 Va 2!	<b>a 1</b> 5 5
5	Glu Val M		ys :60									
	(2) INFORM	ATION FO	R SEQ	ID N	O:74:							
10	(A) (B)	UENCE CI LENGTH TYPE: A	: 260 Amino	amino Acid	ICS: acid	s						
	(xi) SEC	QUENCE D	ESCRIP	: NOIT	SEQ	ID NO	74:					
	Leu Lys 1	Ile Ala	Ala Ph 5	ne Asn	lle	Gln 7	Thr P	he G	ly G	lu T	hr I	ys 15
15	Met Ser	Asn Ala	Thr Le	eu Val	. Ser	Tyr	lle V 25	al G	ln I	le I	.eu S	Ser 30
	Arg Tyr	Asp Ile	Ala Le	eu Val	l Gln	Glu '	Val A	rg A	sp S	Ser F	lis :	Leu 45
20	Thr Ala	Val Gly	Lys L	eu Lei	u Asp	Asn	Leu <i>F</i> 55	sn G	ln A	Asp A	Ala	Pro 60
	Asp Thr	Tyr His	Tyr V	al Va	l Ser	Glu	Pro I	Leu G	Sly A	Arg .	Asn	Ser 75
	Tyr Lys	Glu Arg	Tyr L	eu Ph	e Val	Tyr	Arg 1	Pro P	Asp (	Gln	Val	Ser 90
25	Ala Val	Asp Ser	Tyr 1	Гуг Ту	r Asp	Asp	Gly 100	Cys (	Glu	Pro	Cys	Gly 105
	Asn Asp	Thr Phe	Asn A	Arg Gl	u Pro	Met.	Ile 115	val .	Arg	Phe	Phe	<b>Ser</b> 120
30	Arg Phe	Thr Glu	Val 1	Arg G	lu Phe	e Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala Pro	Gly Ası	Ala 140	Val A	la Gl	u Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr Leu	ı Asp Val	l Gln 155	Glu L	ys Tr	p Gly	Leu 160	Glu	Asp	Val	Met.	Leu 165
35	Met Gly	/ Asp Ph	e Asn 170	Ala G	1у Су	s Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp Se:	r Ser Il	e Arg 185	Leu T	rp Th	ır Sei	Pro 190	Thr	Phe	Glr	Trp	195

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	Ile 1	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr 7	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
5	Val 1	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu S	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	Hıs	Tyr	Pro	Val 255
10	Glu '	Val	Met	Leu	Lys 260										
	(2) 11	NFOR	MATI	ON E	FOR S	SEQ I	D NO	D: <b>7</b> 5	:						
15	(i	( A	L) LE	ENGTE (PE :	1: 26 Amir	ACTER 50 am 10 Ac Line	nino cid	CS: acio	is						
	(xi	) SE	QUE	ICE I	DESC	RIPTI	ON:	SEQ	ID 1	NO : 75	5:				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
20	Met :	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg '	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	<b>Leu</b> 45
	Thr .	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
25	Asp '	Thr	Tyr	His	Туг 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
30	Ala	Val	Asp	Ser	Туг 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn .	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Gln	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Prc	Leu	His	Ala 135
35	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	<b>As</b> p	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165

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		ASI	Pne	170	Ala	Gly	Cys	Ser	<b>Tyr</b> 175	Val	Arg	Pro	Ser	Gln 180
	Trp Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
5	Ile Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
10	Val Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu Val	Mét	Leu	Lys 260										
15	(2) INFO	RMAT:	I NO	FOR S	SEQ :	ID N	0:76	:						
	(,	EQUEI A) LI B) T D) T	ENGTI (PE :	H: 26 Amir	50 ar	mino cid		is						
20	(xi) S	EQUE	NCE I	DESC	RIPT	ION:	SEQ	ID 1	10:76	5:				
	Leu Lys	tlo	בות	77-	Dho	7	_			<b>D</b> -				
	1	116	Ald	5	FILE	Asn	Ile	Gln	Thr 10	Pne	GIY	Glu	Thr	Lys 15
				5					10					15
25	1	Asn	Ala	5 Thr 20	Leu	Val	Ser	Tyr	10 Ile 25	Val	Gln	Ile	Leu	15 Ser 30
25	1 Met Ser	Asn Asp	Ala	Thr 20 Ala 35	Leu Leu	Val	Ser Gln	Tyr Glu	10 Ile 25 Val 40	Val Arg	Gln Asp	Ile Ser	Leu His	15 Ser 30 Leu 45
25	1 Met Ser Arg Tyr	Asn Asp Val	Ala Ile Gly	Thr 20 Ala 35 Lys 50	Leu Leu Leu	Val Val Leu	Ser Gln <b>As</b> p	Tyr Glu Asn	10 Ile 25 Val 40 Leu 55	Val Arg Asn	Gln Asp Gln	Ile Ser Asp	Leu His Ala	15 Ser 30 Leu 45 Pro 60
	Met Ser Arg Tyr Thr Ala	Asn Asp Val	Ala Ile Gly His	5 Thr 20 Ala 35 Lys 50 Tyr 65	Leu Leu Leu Val	Val Val Leu Val	Ser Gln <b>As</b> p Ser	Tyr Glu Asn Glu	10 Ile 25 Val 40 Leu 55 Pro 70	Val Arg Asn Leu	Gln Asp Gln	Ile Ser Asp	Leu His Ala Asn	15 Ser 30 Leu 45 Pro 60 Ser 75
	Met Ser Arg Tyr Thr Ala Asp Thr	Asn Asp Val Tyr	Ala Ile Gly His	Thr 20 Ala 35 Lys 50 Tyr 65 Tyr 80	Leu Leu Val	Val  Val  Val	Ser Gln Asp Ser Val	Tyr Glu Asn Glu Tyr	10 Ile 25 Val 40 Leu 55 Pro 70 Arg 85	Val Arg Asn Leu Pro	Gln Asp Gln Gly Asp	Ile Ser Asp Arg	Leu His Ala Asn Val	15 Ser 30 Leu 45 Pro 60 Ser 75 Ser 90
	Met Ser Arg Tyr Thr Ala Asp Thr	Asn Asp Val Tyr Glu Asp	Ala Ile Gly His Arg	Thr 20 Ala 35 Lys 50 Tyr 65 Tyr 80 Tyr 95	Leu Leu Val Leu	Val Leu Val Phe	Ser Gln Asp Ser Val	Tyr Glu Asn Glu Tyr	10 Ile 25 Val 40 Leu 55 Pro 70 Arg 85 Gly 100	Val Arg Asn Leu Pro	Gln Asp Gln Gly Asp Glu	Ile Ser Asp Arg Gln	Leu His Ala Asn Val	15 Ser 30 Leu 45 Pro 60 Ser 75 Ser 90 Gly105

										145	•				Val 150
	Tyr	Leu	Asp	Val	Gln 155	Gli	u Ly:	s Tr	p Gl	y Leu 160	Glu	Asp	Val	Met	Leu 165
5	Met	Gly	Asp	Phe	Asn 170	Alā	a Gly	/ Cys	s Sei	r Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	: Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
10	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr i	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val 1	Pro .	Asp	Ser	<b>Ala</b> 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 2 <b>4</b> 0
15	Leu S	Ser 1	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu V	al N	let :		Lys 260										
	(2) IN	FORM	LATIO	ON F	OR S	EQ I	D NO	):77:							
20	(i)	(A)	LE)	NGTH PE: 2	HARA : 26 Amino GY: 1	am Ac	ino id	CS: acid	al						
	(xi)	SEQ	UENC	E DI	ESCRI	PTI	ON:	SEQ	ID N	10:77	:				
25	Leu Ly	ys I	le A	la 1	Ala P	he .	Asn	Ile	Gln	Thr I	Phe 0	Sly G	lu T	hr I	Lys 15
	Met Se	er A	sn A	la 1	hr L 20	eu '	Val .	Ser'	Tyr	Ile V 25	al G	ln I	le L	eu S	Ser 30
30	Arg Ty	r As	sp I	le A	la L 35	eu 1	Val (	Gln (	3lu '	Val A 40	rg A	sp S	er H	is L	eu 45
	Thr Al	a Vá	il G	ly L	ys L 50	eu I	Leu A	Asp A	Asn I	Leu A 55	sn G	ln A	sp Al		<b>r</b> o 60
	Asp Th	г ту	т H:	is T	yr V. 65	al V	/al S	er G	Slu P	Pro L	eu G	ly Ai	rg As		<b>e</b> r 75
35	Tyr Ly	9 Gl	u Ai	rg T	yr Le Bo	eu P	he V	al T	yr A	arg P: 85	ro As	sp Gl	.n Va		er 90
	Ala Val	l As	p Se	er Ty	yr Ty 95	r T	yr A	sp A		1y Cy 00	/s Gl	u Pr	с Су		l y 05

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	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Trp	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
5	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
10	Met	Gly	Asp	Phe	<b>As</b> n 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200		Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
15	Tyr	Asp	Arg	Ile	215		Ala	Gly	Met	Leu 220		Arg	Gly	Ala	Val 225
	Val	. Pro	asp	Ser	230		ı Pro	Phe	e Asn	235		Ala	Ala	Tyr	Gly 240
20	Lev	ı Sei	r Asp	Glr	1 Let 245		a Glr	n Ala	a Ile	Ser 250		His	туг	r Pro	255
	Gli	ı Va	l Met	. Le	26										
	(2)	INF	or <b>ma</b> ʻ	TION	FOR	SEQ	ID 1	NO : 7	8:						
25		(i)	(B)	L <b>EN</b> G TYPE	TH: : Am	260 ino	ERIS' amin Acid near								
	(	xi)	SEQU	ENCE	DES	CRIP	TION	: SE	Q ID	NO:	78:				
30	Le	u Ly 1	s Il	e Al	a Al	a Ph 5	e As	n Il	e Gl	n Th 1		e Gl	y Gl	u Th	r Lys 15
	Me	t S€	er As	n Al		r Le	u Va	.l S∈	er Ty		e Va 5	l Gl	n Il	e Le	u Ser 30
	Aı	g Ty	yr As	sp Il		a Le 35	eu Va	il Gl	n Gl		1 Ar	g As	p Se	r Hi	s Leu 45
35	Tì	nr A	la Va	al G		/s Le	eu Le	eu A:	sp As	n Le	u As	n Gl	n As	sp Al	a Pro
	A	sp T	hr T	yr H		yr V. 65	al Va	al S	er G		:0 Le	eu Gl	ly Ai	rg As	sn Ser 75

	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Se:
	Ala	Val	Asp	Ser	Туг 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gl y 105
5	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Tyr	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
10	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	туг	Asp	Val
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Let 165
	Met	Gly	Asp	Phe	<b>As</b> n 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
15	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
20	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	туr	Pro	Val 255
25	Glu	Val	Met	Leu	Lys 260										
	(2)	INFO	RMATI	ON I	FOR S	SEQ 1	ID NO	79	:						
30	( :	( ) ( )	EQUEN A) LE B) TY D) TO	ENGTI (PE :	H: 26 Amir	50 an	nino cid		ds						
	(xi	i) SI	EQUE1	ICE I	ESCF	RIPTI	ON:	SEQ	ID 1	10:79	) :				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
35	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val	Arg	Asp	Ser	Asn	Leu 45

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	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
5	туr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	qaA	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
10	Asn	Asp	Thr	Phe	<b>Asn</b> 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
15	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	L <b>e</b> u 165
	Met	Gly	Asp	Phe	<b>As</b> n 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
20	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	<b>A</b> la 200	<b>As</b> p	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215		Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
25	Val	. Pro	Asp	Ser	Ala 230		Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Lev	ı Ser	raA :	Gln	Leu 245		Gln	Ala	Ile	Ser 250		His	Туг	Pro	<b>Val</b> 255
30	Glu	ı Val	l Met	Lev	260										
	(2)	INF	OR <b>MA1</b>	пои	FOR	SEQ	ID N	10:80	):						
35			SEQUE (A) I (B) I	LENG: TYPE	TH: I	260 a	amino Acid								
	(:	xı)	SEQUI	ENCE	DES	CRIP	rion	SE(	dI C	NO : 6	10:				
		u Ly 1	s Il	e Ala		a Phe	e Ası	7 Ile	e Glr	n Thr		e Gly	y Gl	ı Th:	Lys 15

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	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25		Gln	Ile	Leu	Se:
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40		Asp	Ser	His	Le:
5	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Thr	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	S <b>e</b> 1
10	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	<b>As</b> n 110	Arg	Glu	Pro	Ala	11e 115	Val	Arg	Phe	Phe	Ser 120
15	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
20	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
25	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
30	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 2 <b>4</b> 5	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										

# 35 (2) INFORMATION FOR SEQ ID NO:81:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 260 amino acids
  - (B) TYPE: Amino Acid
  - (D) TOPOLOGY: Linear

	(xi	) SE	QUEN	ICE D	ESCR	IPTI	ON:	SEQ	ID N	10:81	. :				
	Leu 1	Lys	Ile	Ala	Ala 1	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
5	Met	Ser	Asn	Ala	Thr :	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
10	Asp	Thr	Tyr	Asn	Tyr 65	Thr	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
15	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115		Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	. Ile 130		Pro	Leu	His	Ala 135
20	Ala	Pro	Gly	/ Asp	Ala 140	Val	Ala	Glu	Ile	145		Leu	Туг	Asp	Val 150
	Tyr	Leu	ı Asp	o Val	Gln 155	Glu	Lys	Trp	Gly	/ Leu		Asp	Val	Met	Leu 165
25	Met	Gly	/ Ası	o Phe	Asn 170	Ala	a Gly	Cys	s Sei	Tyr 175		Arg	Pro	Ser	Gln 180
	Trp	Sei	r Se	r Ile	e Arg		ı Trp	Thi	r Sei	r Pro		Phe	Glr	Trp	195
	Il€	e Pro	o As	p Sei	r Ala		p Thi	Th	r Ala	a Th:		o Thi	His	s Cys	210
3 C	Туз	r As	p Ar	g Il	e Val		l Ala	a Gl	y <b>M</b> e	t Le <sup>.</sup> 22		ı Arg	g Gl	y Ala	a Val 225
	Va:	l Pr	o As	p Se	r Ala 230		u Pro	o Ph	e As	n Ph 23		n Ala	a Al	а Ту:	r Gly 240
35	Le	u Se	r As	sp Gl	n Let 245		a Gl:	n Al	a Il	e Se 25		p Hi	в Ту	r Pr	o Val 255
	Gl	u Va	.l M∈	et Le	u Ly: 26										

260

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH 260 amino acids (B) TYPE: Amino Acid (D) TCPOLOGY: Linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:82: 5 Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys 5 Met Ser Asn Ala Thr Leu Val Ser Tyr Ile Val Gln Ile Leu Ser Arg Tyr Asp Ile Ala Leu Val Gln Glu Val Arg Asp Ser His Leu 10 Thr Ala Val Gly Lys Leu Leu Asp Asn Leu Asn Gln Asp Ala Pro Asp Thr Tyr His Asn Val Thr Ser Glu Pro Leu Gly Arg Asn Ser 15 Tyr Lys Glu Arg Tyr Leu Phe Val Tyr Arg Pro Asp Gln Val Ser Ala Val Asp Ser Tyr Tyr Tyr Asp Asp Gly Cys Glu Pro Cys Gly Asn Asp Thr Phe Asn Arg Glu Pro Ala Ile Val Arg Phe Phe Ser 20 115 Arg Phe Thr Glu Val Arg Glu Phe Ala Ile Val Pro Leu His Ala 130 Ala Pro Gly Asp Ala Val Ala Glu Ile Asp Ala Leu Tyr Asp Val 25 140 Tyr Leu Asp Val Gln Glu Lys Trp Gly Leu Glu Asp Val Met Leu Met Gly Asp Phe Asn Ala Gly Cys Ser Tyr Val Arg Pro Ser Gln 170 30 Trp Ser Ser Ile Arg Leu Trp Thr Ser Pro Thr Phe Gln Trp Leu Ile Pro Asp Ser Ala Asp Thr Thr Ala Thr Pro Thr His Cys Ala Tyr Asp Arg Ile Val Val Ala Gly Met Leu Leu Arg Gly Ala Val 35 215 Val Pro Asp Ser Ala Leu Pro Phe Asn Phe Gln Ala Ala Tyr Gly Leu Ser Asp Gln Leu Ala Gln Ala Ile Ser Asp His Tyr Pro Val

245

Glu Val Met Leu Lys 260

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### (2) INFORMATION FOR SEQ ID NC:83:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 260 amino acids
  - (B) TYPE: Amino Acid
  - (D) TOPOLOGY: Linear

#### (xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

10	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	туr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
15	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Asn	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
20	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	qeA	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
25	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	<b>Va</b> l
30	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Prc 190	Thr	Phe	Gln	Trp	Leu 195
35	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	туг	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225

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	vai	PIO	Asp	ser	230	Leu	PIO	Pne	Asn	235	GIn	Ala	Ala	Tyr	240
	Leu	Ser	Asp	Gln	Leu 2 <b>4</b> 5	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
5	Glu	Val	Met	Leu	Lys 260										
	(2)	INFO	RMAT:	гои і	FOR S	SEQ :	ID N	0:84	:						
10	(:	(2		ENGT		50 <b>a</b> r	nino		ds						
		(1	) <b>T</b> (	OPOLO	OGY :	Line	ear								
	( x :	i) SI	EQUE	VCE I	DESC	RIPT	ION:	SEQ	ID 1	NO : 84	4:				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
15	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	L <b>e</b> u 45
20	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Asn	Ser	Thr	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	туг	Arg 85	Pro	Asp	Gln	Val	Ser 90
25	Ala	Val	Asp	Ser	Туг 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	<b>As</b> n	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser
3 C	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	<b>As</b> p	Ala	Leu	Tyr	Asp	<b>Va</b> l
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
35	Met	Gly	Asp	Phe	<b>As</b> n 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg	Leu	Trp	Thr	Ser	Prc 190	Thr	Phe	Gln	Trp	Leu 195

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	lle	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Суѕ	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	$Gl_Y$	Ala	Val 225
5	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
10	Glu	Val	Met	Leu	Lys 260										
	(2)	INFO	RMAT:	ION I	FOR S	SEQ :	ID NO	0:85	:						
15	( :	( ) ( )	A) LI B) T	ENGTI YPE :	H: 26 Amir				is						
	(x:	i) SI	EQUE	NCE I	DESCI	RIPT	ION:	SEQ	ID 1	10 : 8 !	5 :				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
20	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	<b>Le</b> u <b>4</b> 5
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
25	Asp	Thr	Tyr	His	<b>Tyr</b> 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
30	Ala	Val	Asp	Asn	Tyr 95	Thr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	<b>A</b> sn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
35	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Glγ	Leu 160	Glu	Asp	Val	Met	Leu 165

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	Met	Gly	Asp	Phe	<b>Asn</b> 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
5	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
10	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										
15	(2)	INFO	RMAT:	I NOI	FOR S	SEQ :	ID N	D: <b>8</b> 6	:						
		() (1 (1	D) TO	ENGTI PE:	H: 26 Amir DGY:	50 ar 10 Ac Line	mino cid ear	acio							
20	( <b>x</b> :	1) SI	EQUEI	ACE I	DESCI	RIPT	ION:	SEQ	ID 1	10:86	5 :				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
25	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	<b>Val 4</b> 0	Arg	Asp	Ser	Glu	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	<b>Le</b> u 55	Asn	Gln	Asp	Ala	Pro 60
30	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
35	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val	Arg	Glu	Phe	Ala	Ile	Val	Pro	Leu	Hıs	Ala 135

	Ald	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	<b>Asp</b> 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
5	Met	Gly	Asp	Phe	<b>As</b> n 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
10	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
15	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										
	(2)	INFO	ריי א אס	COM 1	COD 6	2 <b>E</b> O .	TD M	<b>5.07</b>							
	\-/		RUMATI	LOM	CR	JEQ .	ID N	J: <b>6</b> 7	:						
20		i) Si (i	EQUE1 A) LI	nce ( engt) (pe:	CHARA H: 26 Amii	ACTE	RIST mino cid	ICS:							
20	(:	i) S! (! (!	EQUENA) LI	NCE ( ENGT) (PE:	CHARI H: 26 Amii OGY:	ACTE 60 at no A	RIST mino cid ear	ICS: aci	ds	NO : 8	7:				
20 25	(: (x	i) s: (; ()	EQUENA) LIB) TY	NCE ( ENGT) (PE: OPOL(	CHARI H: 26 Amii OGY: DESCI	ACTE 60 at no Ac Line	RIST mino cid ear ION:	ICS: aci	ds ID			Gly	Glu	Thr	Lys 15
	(x Leu 1	i) Si (i (i t) Si	EQUENA) LI B) TO D) TO	NCE ( ENGTI (PE: DPOL( NCE ) Ala	CHARA H: 26 Amin OGY: DESCI Ala 5	ACTE 60 as no A Line RIPT Phe	RIST mino cid ear ION:	ICS: aci SEQ Ile	<b>ds</b> ID Gln	Thr 10	Phe	•			15
	(x Leu 1 Met	i) Si (1 (1 (1 (1 (1 (1 (1 (1 (1 (1 (1 (1 (1	EQUER A) LI B) TY D) TO EQUER	NCE (PE: DPOLG ) NCE ) Ala	CHARI H: 26 Amii OGY: DESCI Ala 5 Thr 20	ACTE 50 at no A Line RIPT Phe Leu	RIST mino cid ear ION: Asn Val	SEQ Ile	ID Gln Tyr	Thr 10 Ile 25	Phe Val	Gln	Ile	Leu	15 Ser 30
25	(x Leu 1 Met	i) Si () (i) (ii) Si Lys Ser	EQUERA) LH B) TY D) TO EQUER  Ile  Asn	NCE (PENGTI) (PE: (PE: (POPOL) (NCE )	CHARAMINATION CONTROL OF CONTROL	ACTEI 60 am no Am Line RIPT Phe Leu Leu	RIST mino cid ear ION: Asn Val	ICS: aci SEQ Ile Ser	ds ID Gln Tyr	Thr 10 Ile 25 Val 40	Phe Val Arg	Gln	Ile	<b>Le</b> u His	15 Ser 30 Leu 45
25	(x Leu 1 Met Arg	i) Si (i) (ii) Si Lys Ser Tyr	EQUERA) LIB B) TY D) TO EQUER Ile Asn Asp	NCE (CENGTI)  YPE: DPOLCO  Ala  Ala  Ile  Gly	CHARMENT OF THE CONTROL OF THE CONTR	ACTEI 50 am Lind Lind RIPT Phe Leu Leu	RIST mino cid ear ION: Asn Val Val	SEQ Ile Ser Gln	ID Gln Tyr Glu Asn	Thr 10 Ile 25 Val 40 Leu 55	Phe Val Arg Asn	Gln Asp	Ile Ser Asp	Leu His Ala	15 Ser 30 Leu 45 Pro 60
25	(x Leu 1 Met Arg Thr	i) Si (i) (i) (i) Si Lys Ser Tyr Ala	EQUERA) LIBB) TYOUTH TO THE QUERA AS A S P	NCE (PE: OPOLO NCE ) Ala Ala Ile Gly	CHARI H: 26 Amin OGY: DESCI Ala 5 Thr 20 Ala 35 Lys 50 Glu 65	ACTEI 50 at no Ac Line RIPT Phe Leu Leu	RIST mino cid ear ION: Asn Val Val	ICS: aci  SEQ Ile Ser Gln Asp	ds  ID  Gln  Tyr  Glu  Asn	Thr 10 Ile 25 Val 40 Leu 55	Phe Val Arg Asn Leu	Gln Asp Gln	Ile Ser Asp	Leu His Ala Asn	15 Ser 30 Leu 45 Pro 60 Ser 75

Asn Asp Thr Phe Asn Arg Glu Pro Ala Ile Val Arg Phe Phe Ser

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	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
5	Ala	Pro	Gly	Asp	Ala 1 <b>4</b> 0	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
10	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
15	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	V <b>a</b> l 2 <b>2</b> 5
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 2 <b>4</b> 0
20	Leu	Ser	Asp	Gln	Leu 2 <b>4</b> 5	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										
	(2)	INFO	RMAT:	ION 1	FOR S	SEQ :	ID N	88:0	:						
25	(	(1	A) LI B) T	ENGTI YPE :	CHARA H: 26 Amir DGY:	50 ar 10 Ad	mino cid		ds						
	( <b>x</b>	i) SI	EQUE	NCE I	DESC	RIPT	ON:	SEQ	ID 1	10 : 88	3 :				
30	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	Ala	Leu 45
35	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Arg	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Ala 65	Val	Val	Ser	Arg	Pro 70	Leu	Gly	Arg	Asn	Ser 75

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	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Туг 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
5	Asn	Asp	Thr	Phe	<b>As</b> n 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
10	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	<b>As</b> p	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
15	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	qaA	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
20	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	туr	Pro	Val 255
25	Glu	Val	Met	Leu	Lys 260										
	(2)	INFO	RMAT	ION	FOR .	SEQ	ID N	0:89	:						
30	(	(	B) T	ENGT YPE :		60 a no A			ds						
	( x	i) S	EQUE	NCE	DESC	RIPT	ION:	SEQ	ID	NO : 8	9 :				
	Leu 1	-	Ile	Ala	Ala 5		Asn	Ile	Gln	Thr 10		Gly	Glu	Thr	Lys 15
35	Met	Ser	Asn	Ala	Thr 20		Val	Ser	Tyr	Ile 25		Gln	Ile	Leu	Ser 30
	Arg	Туг	Asp	Ile	Ala 35		Val	Gln	Glu	Val 40	_	Asp	Ser	His	Leu 45

	Thr	Ala	Arg	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	naA	Ser 75
5	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	qeA	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gl <sub>y</sub> 100	Cys	Glu	Pro	Cys	Gly 105
10	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	11e 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	11e 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
15	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
20	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
25	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	туг	Pro	Val 255
30	Glu	Val	Met	Leu	Lys 260										
	(2)	INFO	RMAT:	ION 1	FOR S	SEQ :	ID N	): <b>9</b> 0	:						
<b>3</b> 5	(:	() {1	EQUE A) Li B) T D) T	ENGTI YPE :	H: 20 Amir	50 ar 10 Ac	mino cid		ds						
	( <b>x</b> :	i) Si	EQUEI	VCE I	DESCI	RIPT	ION:	SEQ	ID 1	10 : 9 (	0 ;				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr	Phe	Gly	Glu	Thr	Lys 15

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	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
5	Thr	Ala	Val	Gly	Lys 50	Leu	Asn	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
10	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
15	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	Hıs	Ala 135
	Ala	Pro	Gly	qeA	Ala 140	Val	Ala	Glu	Ile	<b>Asp</b>	Ala	Leu	Tyr	Asp	<b>Va</b> l
20	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	<b>Le</b> u 195
25	Ile	Pro	Asp	Ser	<b>Ala</b> 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
30	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										

- 35 (2) INFORMATION FOR SEQ ID NO:91:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 260 amine acids
      (B) TYPE: Amino Acid

    - (D) TOPOLOGY: Linear

(xi)	SEQUENCE	DESCRIPTION:	SEO	ID	NO:91:
------	----------	--------------	-----	----	--------

	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr	Phe	Gly	Glu	Thr	Lys 15
5	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Arg	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Prc 60
10	Asp	Thr	Tyr	His	Туг 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
15	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	<b>Asn</b> 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	Hıs	Ala 135
20	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	<b>Asp</b> 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	<b>Le</b> u 160	Glu	Asp	Val	Met	Leu 165
25	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
30	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
35	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
					- • -					230					<b>£</b> 33

(2) INFORMATION FOR SEQ ID NO:92:

WO 96/26279

	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 260 amino acids</li><li>(B) TYPE: Amino Acid</li><li>(D) TOPOLOGY: Linear</li></ul>	
5	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:	
	Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys 1 5 10 15	
	Met Ser Asn Ala Thr Leu Val Ser Tyr Ile Val Gln Ile Leu Ser 20 25 30	
10	Arg Tyr Asp Ile Ala Leu Val Gln Glu Val Arg Asp Ser His Leu 35 40 45	
	Thr Ala Val Gly Lys Leu Leu Asp Asn Leu Cys Gln Asp Ala Pro 50 55 60	
15	Asp Thr Tyr His Tyr Val Val Ser Glu Pro Leu Gly Arg Asn Ser 65 70 75	
	Tyr Lys Glu Arg Tyr Leu Phe Val Tyr Arg Pro Asp Gln Val Ser	
	Ala Val Asp Ser Tyr Tyr Tyr Asp Asp Gly Cys Glu Pro Cys Gly 95 100 105	
20	Asn Asp Thr Phe Asn Arg Glu Pro Ala Ile Val Arg Phe Phe Ser 110 115 120	)
	Arg Phe Thr Glu Val Arg Glu Phe Ala Ile Val Pro Leu His Ala 125 130	<b>i</b>
25	Ala Pro Gly Asp Ala Val Ala Glu Ile Asp Ala Leu Tyr Asp Val	) C
	Tyr Leu Asp Val Gln Glu Lys Trp Gly Leu Glu Asp Val Met Let 155 160 169	1 5
	Met Gly Asp Phe Asn Ala Gly Cys Ser Tyr Val Arg Pro Ser Gl:	n 0
30	Trp Ser Ser Ile Arg Leu Trp Thr Ser Pro Thr Phe Gln Trp Le 185 190 19	u 5
	Ile Pro Asp Ser Ala Asp Thr Thr Ala Thr Pro Thr His Cys Al 200 205 21	a 0
35	Tyr Asp Arg Ile Val Val Ala Gly Met Leu Leu Arg Gly Ala Va 215 220	11 25
	Val Pro Asp Ser Ala Leu Pro Phe Asn Phe Gln Ala Ala Tyr Gl 230 235 24	L y 1 0
	Leu Ser Asp Gln Leu Ala Gln Ala Ile Ser Asp His Tyr Pro Va 245 250 29	a 1 5 5

Glu Val Met Leu Lys 260

## (2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 260 amino acids

(B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

# (xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

	( )	1, 5	EQUE.	NCE	DESC	KIPI	TON:	SEQ	ID	NO : 9	3:				
10	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	<b>Va</b> l	Arg	Asp	Ser	His	Leu 45
15	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	<b>Le</b> u <b>5</b> 5	Phe	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
20	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	qeA	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
25	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
30	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	qeA	Phe	<b>As</b> n 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	<b>Le</b> u 195
35	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	<b>Ala</b> 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225

-123-

5 Gl (2)	lu '			Gln L 2	eu A :45	la G	iln #	Ala :			Asp :	His	Tyr		Val
(2) LO LS M		Val I	Met 1							250					255
LO L	) I			Leu I 2	ys 260										
L 15 M		NFOR	MATI	ON FO	OR SE	EQ II	ON O	: 94 :							
L. 15 M	í)	(A	) LE	CE CH NGTH: PE: 1 POLOG	: 260 Amino	am: Ac:	ino a id		S						
15 M	(xi	) SE	QUEN	CE DI	ESCR:	IPTI	: MC	SEQ	ID N	10 : 94	:				
	eu 1	Lys	Ile	Ala	Ala :	Phe 2	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
A	let	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
T 20	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Lys	Gln	Asp	Ala	Pro 60
A	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
ד	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
25 A	Ala	Val	Asp	Ser	<b>Tyr</b> 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
1	Asn	Asp	Thr	Phe	<b>As</b> n 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
30	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	11e		Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	ı Ile	2 Asp		Leu	ı Tyr	Asp	Val 150
	Туг	Leu	ı Asp	Val	Gln 155	Glu	Lys	Trp	Gly	/ Leu 160		Asp	val	. Met	165
35							Clv		Sei	TV	. Val	l Arc	g Pro	Ser	Glr
	Met	Gly	/ Asp	) Phe	<b>As</b> n 170		Gry	Суз		175					180

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	Ile Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
5	Val Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
10	Glu Val	Met	Leu	Lys 260										
	(2) INFO	RMATI	ON F	FOR S	SEQ :	ID NO	0:95	;						
15	(	EQUEN A) LE B) TY D) TO	NGTH	H: 26 Amir	50 an	mino cid		is						
	(xi) S	EQUEN	ICE I	DESC	RIPT	ION:	SEQ	ID 1	10 : 9 !	5 :				
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20	Met Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	L <b>e</b> u 45
	Thr Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Arg	Gln	Asp	Ala	Pro 60
25	Asp Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
30	Ala Val	Asp	Ser	Туг 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
35	Ala Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	<b>As</b> p	Ala	Leu	Tyr	Asp	<b>Val</b> 150
	Tyr Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165

-125-

	Met Gly As	p Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp Ser Se	r Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
5	Ile Pro As	sp Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr Asp Ai	g Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
10	Val Pro As	sp Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Туг	Gly 2 <b>4</b> 0
	Leu Ser As	sp Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu Val Me	et Leu	Lys 260										
15	(2) INFORM	TION I	FOR S	EQ 1	ID N	0:96	:						
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25	Arg Tyr A	sp Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	L <b>e</b> u 45
	Thr Ala V	al Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Trp	Gln	Asp	Ala	Pro 60
3 C	Asp Thr T	yr His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	S <b>e</b> r 75
	Tyr Lys G	lu Arg	<b>T</b> yr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala Val A	sp Ser	Туг 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
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	Arg Phe T	hr Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135

	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
5	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
10	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Aap	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
15	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	Hıs	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										
	(2)	(NFO	RMAT	ION	FOR S	SEQ :	ID N	0:97	:						
20	( j	(	A) L B) T	ENGT YPE :	CHARI H: 2: Ami: OGY:	60 ai	mino cid		ds						
	( <b>x</b> :	i) S	EQUE	NCE	DESC:	RIPT	ION:	SEQ	ID	<b>N</b> O : 9	7:				
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	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25		Gln	lle	Leu	Ser 30
30	Arg	Tyr	Asp	lle	Ala 35		Val	Gln	Glu	Val		Asp	Ser	His	Leu 45
	Thr	Ala	Val	. Gly	Lys 50		Leu	Asp	Asn	Leu 55		ı Glr	a Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Pro 65		Val	Ser	Glu	Pro 70		ı Gly	/ Arg	Asn	Ser 75
35	Tyr	Lys	s Glu	ı Arg	Tyr 80		Phe	· Val	Tyr	Arg		Asp	o Glm	val	Ser 90
	n1 -		_	_	_	_	Туг		_		_		_	_	G1

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	Asn Asp Thr	Phe Asn	Arg	Glu	Pro	Ala	Ile 115	Val .	Arg	Phe	Phe	Ser 120
	Arg Phe Thr	Glu Val		Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
5	Ala Pro Gly	Asp Ala		Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr Leu Ası	Val Glr 159		Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
10	Met Gly Asp	p Phe Asi		Gly	Суѕ	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp Ser Se	r Ile Are		Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile Pro As	p Ser Al 20		Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
15	Tyr Asp Ar	g Ile Va 21		l Ala	Gly	Met	<b>Le</b> u 220	Leu	Arg	Gly	Ala	Val 225
	Val Pro As	p Ser Al 23		ı Pro	Phe	. Asn	235	Gln	Ala	Ala	Tyr	Gly 240
20	Leu Ser As	sp Gln Le 24		a Glr	n Ala	ı Ile	ser 250	Asp	His	туг	r Pro	255
	Glu Val Me	et Leu Ly 26										
	(2) INFORM	ATION FO	R SEQ	ID 1	NO : 98	B :						
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	Met Ser A	sn Ala T	hr Lo 20	eu Va	l Se	er Ty	r Il 2	e Va 5	l Gl	n Il	e Le	u Ser 30
	Arg Tyr A	Asp Ile A	la L 35	eu Va	ıl Gl	n Gl	u Va 4	1 Ar	g As	sp Se	er Hi	s Leu 45
35	Thr Ala V	Val Gly I	<b>Lys L</b> 50	eu Le	eu As	sp As	sn Le	eu As	n G	ln As	sp Al	la Pro 60
	Asp Thr	Tyr His '	ryr V 65	al Va	al A	sn G	lu Th	nr Le 70	eu G	ly A	rg A	sn Ser 75

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										8 9	5				l Ser 90
					,					100	)				5 Gly 105
5				r Phe	110					115	,				120
	Arg	y Ph	e Th	r Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
10	Ala	Pr	o Gly	y Asp	Ala 140	Val	Ala	Glu	Ile	Asp	Ala	Leu	Tyr	Asp	Val 150
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	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln .	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 2 245	Ala	Gln	Ala	Ile	Ser 250	Asp 1	His '	Tyr :		Val 255
25	Glu	Val	Met	Leu	Lys 260										

PCT/US96/02421 WO 96/26279

#### **Claims**

What is claimed is

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- 1. A human DNase I actin-resistant variant.
- 2. A variant of claim 1 that has a binding affinity for actin that is at least five-fold less than that of native human DNase I. 5
  - 3. A variant of claim 1 that has a binding affinity for actin that is at least 100-fold less than that of native human DNase I.
  - 4. A variant of claim 1 comprising an amino acid sequence having at least 90% identity with the amino acid sequence of native human DNase I shown in Figure 1.
  - 5. A variant of claim 1 comprising an amino acid sequence having at least 95% identity with the amino acid sequence of native human DNase I shown in Figure 1.
    - 6. A human DNase I actin-resistant variant having an amino acid sequence that differs from the amino acid sequence shown in Figure 1 by the substitution of one amino acid for another at only a single position within the Figure 1 sequence.
  - 7. A variant of claim 6 wherein the amino acid substitution creates a glycosylation site within the variant that is not present in native human DNase I.
    - 8. A variant of claim 6 wherein the amino acid substitution is at one of the following positions within the Figure 1 sequence: His44, Leu45, Val48, Gly49, Leu52, Asp53, Asn56, His64, Tyr65, Val66, Val67, Ser68. Glu69, or Alal 14.
    - 9. A human DNase I actin-resistant variant having an amino acid sequence that differs from the amino acid sequence shown in Figure 1 by the substitution of one amino acid for another at two or more positions within the Figure 1 sequence.
    - 10. A variant of claim 9 wherein at least one of the amino acid substitutions is made at one of the following positions within the Figure 1 sequence: His44, Leu45, Val48, Gly49, Leu52, Asp53, Asn56, His64, Tyr65, Val66, Val67, Ser68, Glu69, Ser94, Tyr96, or Ala114.
    - 11. A variant of claim 9 wherein at least one of the amino acid substitutions creates a glycosylation site within the variant that is not present in native human DNase I.
      - 12. An isolated nucleic acid encoding a human DNase I actin-resistant variant.
    - 13. The nucleic acid of claim 12 comprising a nucleotide sequence that encodes an amino acid sequence having at least 90% identity with the amino acid sequence of native human DNase shown in Figure 1.
      - 14. The nucleic acid of claim 12 comprising a nucleotide sequence that encodes an amino acid sequence having at least 95% identity with the amino acid sequence of native human DNase shown in Figure
    - 15 The nucleic acid of claim 12 comprising a nucleotide sequence that encodes an amino acid 1 sequence that differs from the amino acid sequence shown in Figure 1 by the substitution of one amino acid for another at only a single position within the Figure 1 sequence

16. The nucleic acid of claim 12 comprising a nucleotide sequence that encodes an amino acid sequence that differs from the amino acid sequence shown in Figure 1 by the substitution of one amino acid for another at only two positions within the Figure 1 sequence.

- 17. A method for the treatment of a patient having a pulmonary disease or disorder comprising administering to the patient a therapeutically effective amount of an actin-resistant variant of human DNase I
  - 18. The method of claim 17 wherein the disease or disorder is cystic fibrosis.

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- 19. The method of claim 17 wherein the disease or disorder is chronic bronchitis.
- 20. A pharmaceutical composition comprising an actin-resistant variant of human DNase I and optionally a pharmaceutically acceptable excipient.
  - 21. The composition of claim 20 wherein the composition is in liquid form.
  - 22. The composition of claim 21 wherein the composition is in powder form.

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LKIAAFNIQTFGETKMSNATLVSYIVQILSRYDIALVQEVRDSHLTAVGK LLDNLNQDAPDTYHYVVSEPLGRNSYKERYLFVYRPDQVSAVDSYYYDDG CEPCGNDTFNREPAIVRFFSRFTEVREFAIVPLHAAPGDAVAEIDALYDV YLDVQEKWGLEDVMLMGDFNAGCSYVRPSQWSSIRLWTSPTFQWLIPDSA DTTATPTHCAYDRIVVAGMLLRGAVVPDSALPFNFQAAYGLSDQLAQAIS DHYPVEVMLK

FIG. 1

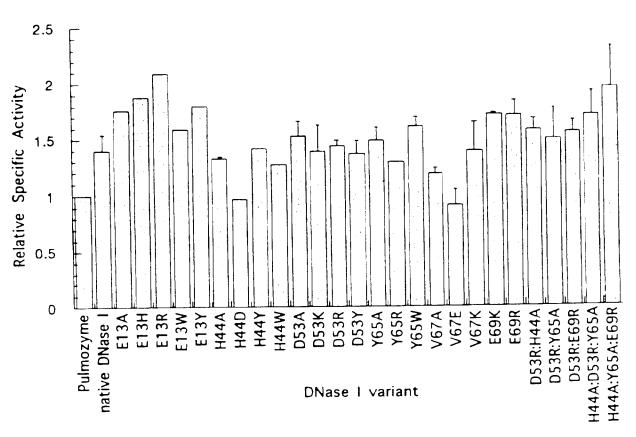


FIG. 2A

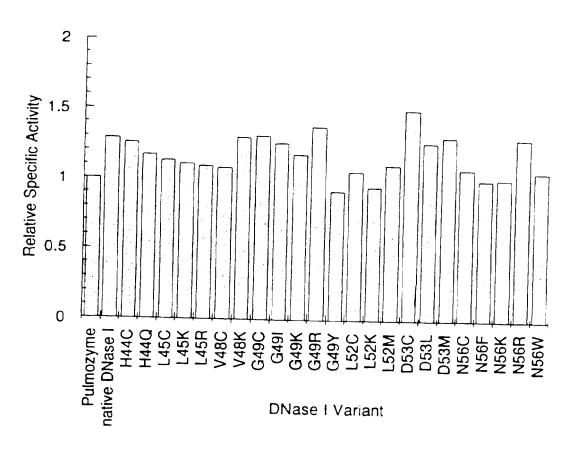


FIG. 2B

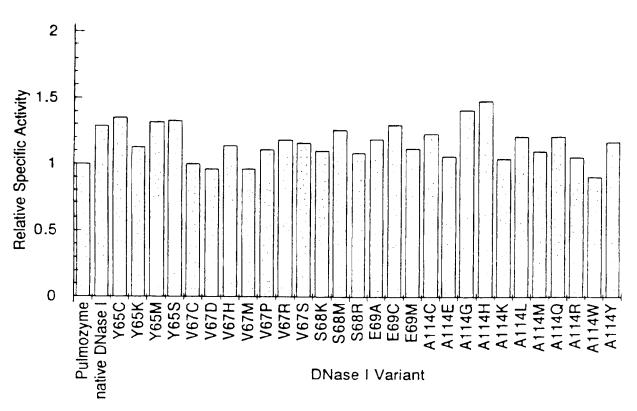
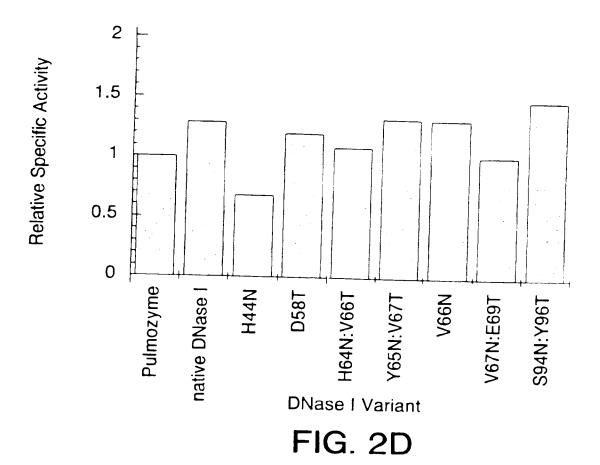
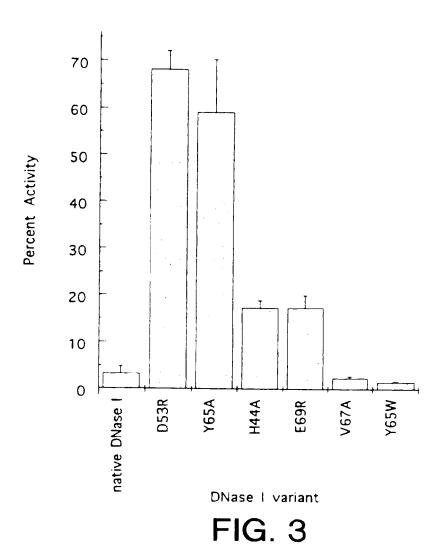


FIG. 2C



**SUBSTITUTE SHEET (RULE 26)** 



**SUBSTITUTE SHEET (RULE 26)** 

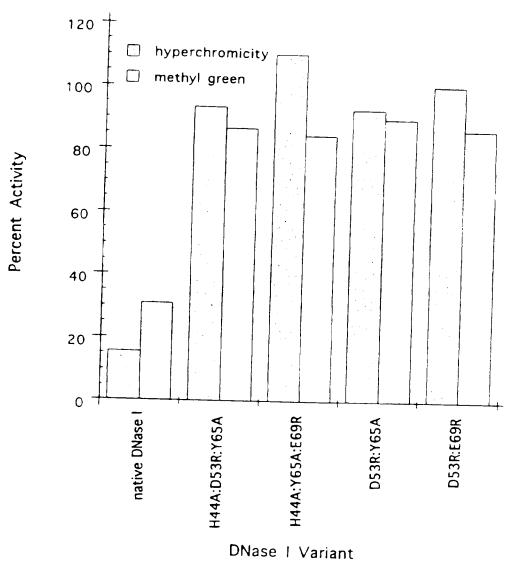


FIG. 4

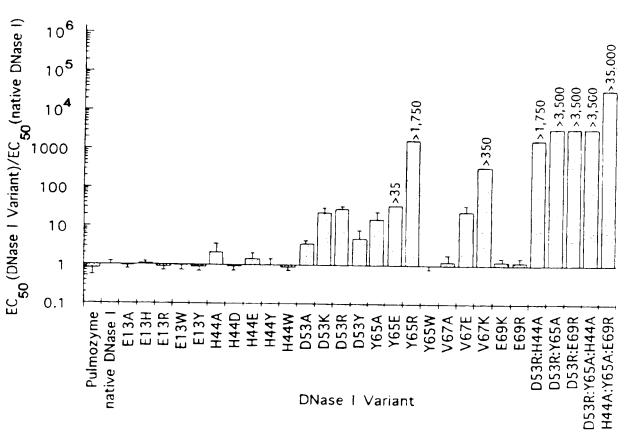


FIG. 5A

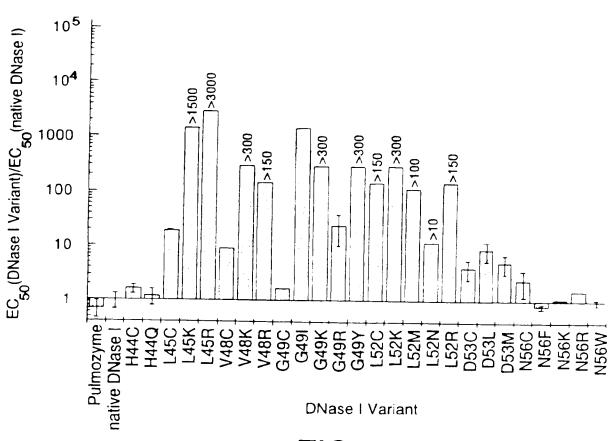


FIG. 5B

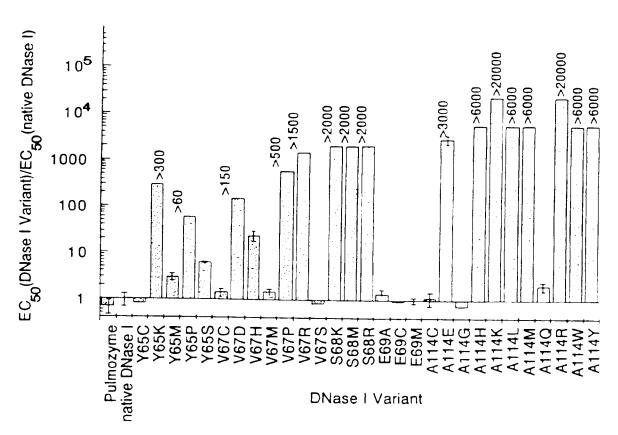


FIG. 5C

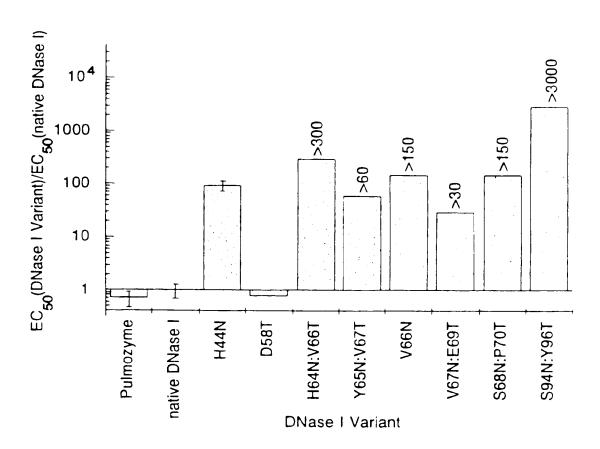
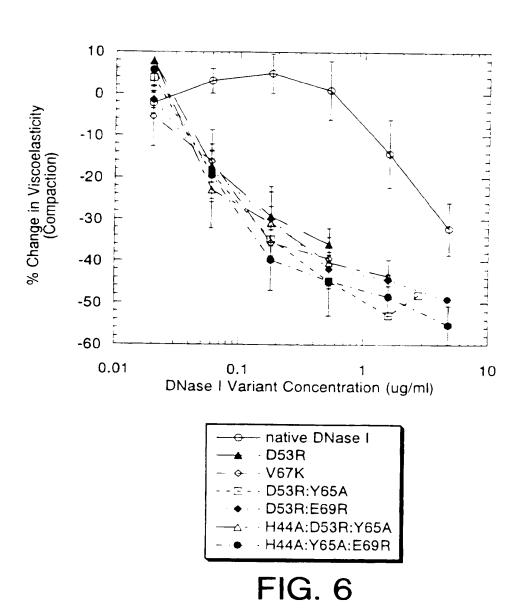


FIG. 5D



**SUBSTITUTE SHEET (RULE 26)** 

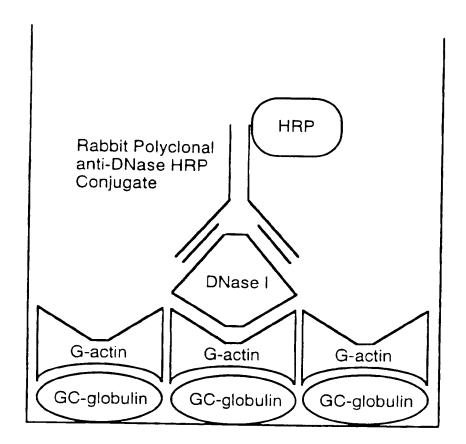


FIG. 7

#### INTERNATIONAL SEARCH REPORT

Internation Application No. PCT/US 96/02421

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C12N15/55 C12N9/22 A61K38/46 According to International Patent Classification (IPC) or to both national classification and IPC **B. FIELDS SEARCHED** Minimum documentation searched (classification system followed by classification symbols) IPC 6 C12N A61K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Relevant to claim No. Category ' Citation of document, with indication, where appropriate, of the relevant passages WO,A,90 07572 (GENENTECH INC) 12 July 1990 1,4-7,9, Χ 11-22 cited in the application see page 3, line 19 - page 6, line 25 see page 16, line 32 - page 17, line 34 see example 5 Y see claims 1,4-7,9,11-22 WO,A,94 22465 (BRIGHAM & WOMENS HOSPITAL) 1,4-7,9, Υ 13 October 1994 11-22 cited in the application see page 7 see page 11, line 7 - page 15, line 28 see examples 4.5 -/--Х Further documents are listed in the continuation of box C. ΙX Patent family members are listed in annex. Special categories of cited documents: "I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the "A" document defining the general state of the art which is not considered to be of particular relevance invention earlier document but published on or after the international "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to filing date "I." document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified). involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such docu-"O" document referring to an oral disclosure, use, exhibition or ments, such combination being obvious to a person skilled other means document published prior to the international filing date but later than the priority date claimed '&' document member of the same patent family Date of the actual completion of the international search Date of mailing of the international search report 25.07.96 18 July 1996 Name and mailing address of the ISA Authorized officer European Patent Office, P.B. 5818 Patentiaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31-651 epo nl, Andres, S

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Fax (+31-70) 340-3016

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Internation Application No PCT/US 96/02421

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C.(Continu Category	auon) DOCUMENTS CONSIDERED TO BE RELEVANT  Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Сасевску	Creation of document, with indication, where appropriate, of the relevant passages	Refevant to claim No.
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A	PROC NATL ACAD SCI U S A 87 (23). 1990. 9188-9192, XP002008764 SHAK, S. ET AL.: "RECOMBINANT HUMAN DNASE I REDUCES THE VISCOSITY OF CYSTIC FIBROSIS SPUTUM." cited in the application	

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In' ation on patent family members

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		EP-A-	0449968	09-10-91
		JP-T-	4502406	07-05-92
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		BR-A-	9405856	05-03-96
		EP-A-	0692970	24-01-96
		GB-A-	2293102	20-03-96
		NO-A-	953862	29-09-95